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Patent and Trademark Office

SEARCH REQUEST FORM

9-149

Requestor's Name: Russell Travers

Serial Number: 08/822,071

Date: 9/4/97 Phone: 308-1603 Art Unit: 1205

Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevent citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevent claim(s).

The compound of claim 46-52 (allowed)

for any Antiviral use (esp HIV)

STAFF USE ONLY

Date completed: 9/5/97

Searcher: —

Terminal time: 45

Elapsed time: _____

CPU time: _____

Total time: 55

Number of Searches: 1

Number of Databases: 3

Search Site

_____ STIC

✓ CM-1

_____ Pre-S

Type of Search

_____ N.A. Sequence

_____ A.A. Sequence

_____ Structure

✓ Bibliographic

Vendors

_____ IG

✓ STN

_____ Dialog

_____ APS

_____ Geninfo

_____ SDC

_____ DARC/Questel

_____ Other

PTO-1590 (9-90)

=> fil reg
FILE 'REGISTRY' ENTERED AT 13:48:06 ON 05 SEP 1997
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STRUCTURE FILE UPDATES: 29 AUG 97 HIGHEST RN 193400-04-3
DICTIONARY FILE UPDATES: 04 SEP 97 HIGHEST RN 193400-04-3

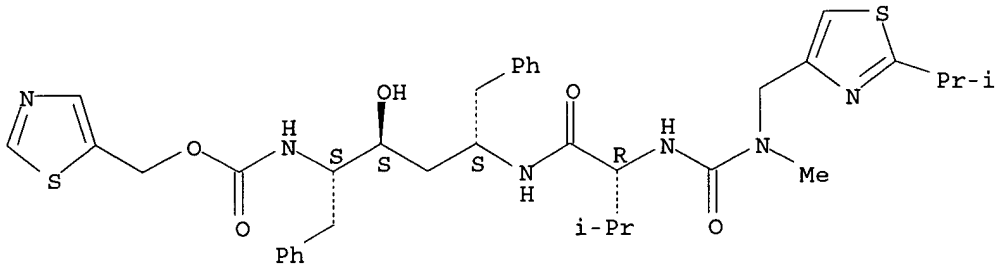
TSCA INFORMATION NOW CURRENT THROUGH DECEMBER 1996

Please note that search-term pricing does apply when conducting SmartSELECT searches.

=> d ide can l20 1-

L20 ANSWER 1 OF 2 REGISTRY COPYRIGHT 1997 ACS
RN 183388-65-0 REGISTRY
CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, [5R-(5R*,8S*,10S*,11S*)]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN A 117673
FS STEREOSEARCH
MF **C37 H48 N6 O5 S2**
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

Absolute stereochemistry.



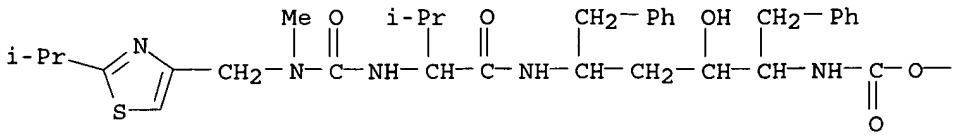
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:301429

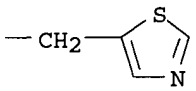
REFERENCE 2: 125:329477

L20 ANSWER 2 OF 2 REGISTRY COPYRIGHT 1997 ACS
RN 162990-01-4 REGISTRY
CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester (9CI) (CA INDEX NAME)
MF **C37 H48 N6 O5 S2**
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

PAGE 1-A



PAGE 1-B



4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 125:301598

REFERENCE 2: 124:87790

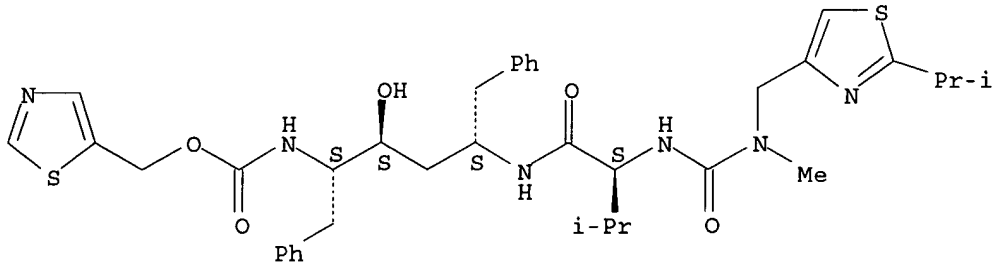
REFERENCE 3: 123:314522

REFERENCE 4: 122:299083

=> d ide can l21 1-

L21 ANSWER 1 OF 1 REGISTRY COPYRIGHT 1997 ACS
RN 155213-67-5 REGISTRY
CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN A 84538
CN Abbott 84538
CN ABT 538
CN Norvir
CN Ritonavir
FS STEREOSEARCH
MF **C37 H48 N6 O5 S2**
CI COM
SR CAS Registry Services
LC STN Files: BIOBUSINESS, BIOSIS, CA, CAPLUS, CEN, CHEMLIST, CIN, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, PHAR, PROMT, TOXLINE, TOXLIT, USAN, USPATFULL

Absolute stereochemistry.



48 REFERENCES IN FILE CA (1967 TO DATE)
48 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:44485

REFERENCE 2: 127:44482

REFERENCE 3: 127:44378

REFERENCE 4: 127:12922

REFERENCE 5: 127:12782

REFERENCE 6: 126:338434

REFERENCE 7: 126:327288

REFERENCE 8: 126:301431

REFERENCE 9: 126:301429

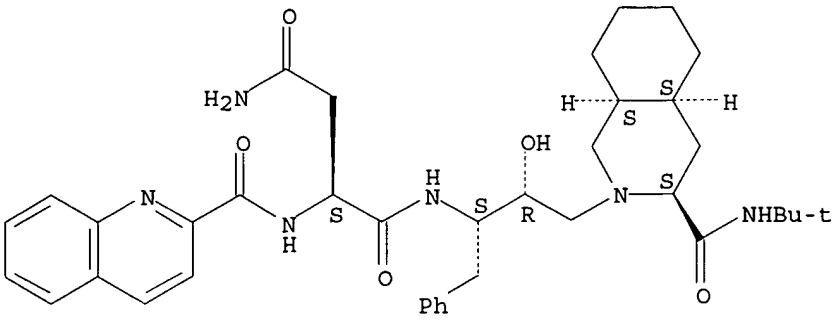
REFERENCE 10: 126:287562

=> d ide can l28

L28 ANSWER 1 OF 1 REGISTRY COPYRIGHT 1997 ACS
RN 127779-20-8 REGISTRY
CN Butanediamide, N1-[3-[3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, [3S-[2[1R*(R*),2S*],3.alpha.,4a.beta.,8a.beta.]]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (S)-N-[(.alpha.S)-.alpha.-[(1R)-2-[(3S,4aS,8aS)-3-(tert-Butylcarbamoyl)octahydro-2(1H)-isoquinolyl]-1-hydroxyethyl]phenethyl]-2-quinaldamidosuccinamide
CN **Ro 31-8959**
CN Ro 31-8959/000
CN Saquinavir
CN Sch 52852
FS STEREOSEARCH
DR 131176-13-1
MF C38 H50 N6 O5
CI COM
SR CA
LC STN Files: AIDSLINE, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAPLUS, CASREACT, CEN, CIN, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, PHAR, PNI, PROMT,

TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.



124 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
124 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:132592

REFERENCE 2: 127:117088

REFERENCE 3: 127:90182

REFERENCE 4: 127:60214

REFERENCE 5: 127:44485

REFERENCE 6: 127:335

REFERENCE 7: 126:338434

REFERENCE 8: 126:327288

REFERENCE 9: 126:301432

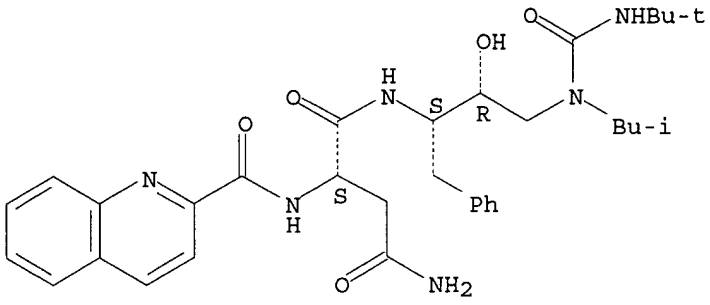
REFERENCE 10: 126:301431

=> d ide can l29

L29 ANSWER 1 OF 1 REGISTRY COPYRIGHT 1997 ACS
RN 143224-34-4 REGISTRY
CN Butanediamide, N1-[3-[[[(1,1-dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, [1S-[1R*(R*),2S*]]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Compound E
CN **SC 52151**
CN Telinavir
FS STEREOSEARCH
MF C33 H44 N6 O5
SR CA

LC STN Files: AGRICOLA, BIOBUSINESS, BIOSIS, CA, CAPLUS, CHEMLIST, DDFU, DRUGU, DRUGUPDATES, EMBASE, IPA, PHAR, TOXLINE, TOXLIT, USAN, USPATFULL
Other Sources: WHO

Absolute stereochemistry.



28 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
29 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:28589

REFERENCE 2: 126:338434

REFERENCE 3: 126:248178

REFERENCE 4: 126:246812

REFERENCE 5: 126:225081

REFERENCE 6: 126:166463

REFERENCE 7: 126:94665

REFERENCE 8: 125:238651

REFERENCE 9: 125:75603

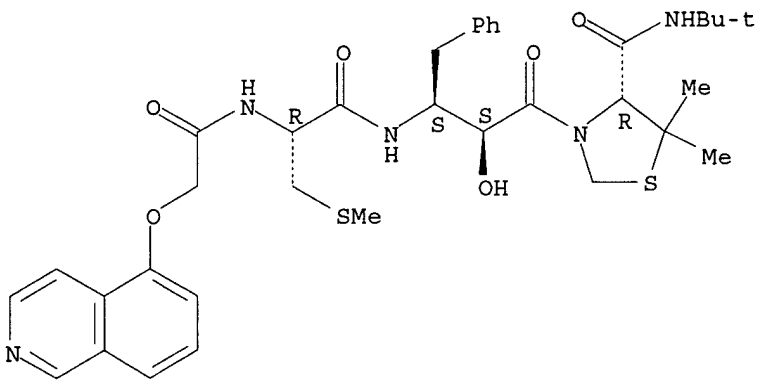
REFERENCE 10: 125:58548

=> d ide can l30

L30 ANSWER 1 OF 1 REGISTRY COPYRIGHT 1997 ACS
RN 147384-69-8 REGISTRY
CN 4-Thiazolidinecarboxamide, N-(1,1-dimethylethyl)-3-[2-hydroxy-3-[[2-[[(5-isoquinolinyloxy)acetyl]amino]-3-(methylthio)-1-oxopropyl]amino]-1-oxo-4-phenylbutyl]-5,5-dimethyl-, [4R-[3[2S*,3S*(R*)],4R*]]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN KNI 2227
CN **KNI 227**
CN Kynostatin 227
FS STEREOSEARCH
MF C35 H45 N5 O6 S2

SR CA
LC STN Files: AIDSLINE, CA, CANCERLIT, CAPLUS, DRUGUPDATES, MEDLINE, PROMT, TOXLIT, USPATFULL

Absolute stereochemistry.



11 REFERENCES IN FILE CA (1967 TO DATE)
11 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:109197

REFERENCE 2: 125:316278

REFERENCE 3: 124:15515

REFERENCE 4: 122:310495

REFERENCE 5: 121:301322

REFERENCE 6: 121:291727

REFERENCE 7: 121:194926

REFERENCE 8: 121:99067

REFERENCE 9: 120:94631

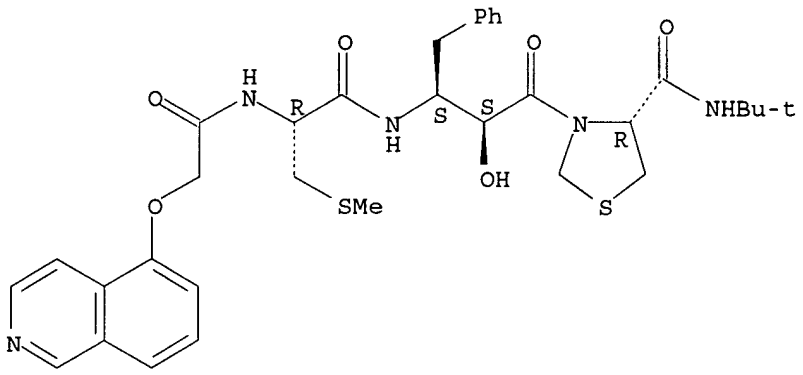
REFERENCE 10: 119:62471

=> d ide can l31

L31 ANSWER 1 OF 1 REGISTRY COPYRIGHT 1997 ACS
RN 147318-81-8 REGISTRY
CN 4-Thiazolidinecarboxamide, N-(1,1-dimethylethyl)-3-[2-hydroxy-3-[[2-[[(5-isoquinolinyloxy)acetyl]amino]-3-(methylthio)-1-oxopropyl]amino]-1-oxo-4-phenylbutyl]-, [4R-[3[2S*,3S*(R*)],4R*]]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **KNI 272**
CN Kynostatin
CN Kynostatin 272
FS STEREOSEARCH
MF C33 H41 N5 O6 S2

CI COM
SR CA
LC STN Files: AIDSLINE, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAPLUS, CASREACT, CIN, DRUGNL, DRUGUPDATES, EMBASE, MEDLINE, PHAR, PROMT, TOXLIT, USPATFULL

Absolute stereochemistry.



46 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
46 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:109197

REFERENCE 2: 126:311810

REFERENCE 3: 126:272344

REFERENCE 4: 126:258544

REFERENCE 5: 126:246812

REFERENCE 6: 126:166463

REFERENCE 7: 126:114991

REFERENCE 8: 126:84118

REFERENCE 9: 126:69590

REFERENCE 10: 126:54427

=> d his l22-l27

(FILE 'HCAPLUS' ENTERED AT 13:29:26 ON 05 SEP 1997)
L22 6 S L20
L23 1 S A()(117673 OR 117 673) OR A117673
L24 6 S L22,L23
L25 77 S L21 OR RITONAVIR OR NORVIR
L26 4 S (A OR ABBOTT)()(84538 OR 84 538)
L27 77 S L22-L26

=> d his l32-

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     (FILE 'HCAPLUS' ENTERED AT 13:35:51 ON 05 SEP 1997)
L32          124 S L28
L33          150 S SAQUINAVIR OR RO 31 8959 OR RO31 8959 OR RO318959
L34          180 S L32,L33
L35           29 S L29
L36           18 S SC()(52151 OR 52 151) OR SC52151
L37           31 S L35,L36
L38           11 S L30
L39           10 S KNI 227 OR KNI227
L40           14 S L38,L39
L41           46 S L31
L42           49 S KNI 272 OR KNI272
L43           55 S L41,L42
L44           42 S L27 AND L34
L45            9 S L27 AND L37
L46            0 S L27 AND L40
L47            8 S L27 AND L43
L48           43 S L44,L45,L47
L49            5 S SYNERG? AND L48
L50           29 S COMBIN? AND L48
L51            2 S COMPOSITION AND L48
L52            6 S L49,L51
L53            6 S L50 AND L52
L54            1 S L48 AND CONCOMIT?
L55            7 S L53,L54
                 E KEMPF D/AU
L56           78 S E3-E7
                 E NORBECK D/AU
L57           64 S E4-E8
                 E SHAM H/AU
L58           63 S E3,E4,E6-E9
                 E ZHAO C/AU
L59          345 S E3-E16,E96-E133
                 E RENO D/AU
L60            8 S E4-E6
                 E SOWIN T/AU
L61           20 S E4-E7
                 E HAIGHT A/AU
L62           13 S E4-E7
L63           13 S L56-L62 AND L27
L64            3 S L63 AND L48
L65            0 S L48 AND COADMINST?
L66            2 S L48 AND COADMINI?
L67           11 S L55,L64,L66
L68           10 S L63 NOT L67
L69           15 S L48 AND INTERACT?
L70           20 S L67,L69

     FILE 'REGISTRY' ENTERED AT 13:48:06 ON 05 SEP 1997

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 13:49:31 ON 05 SEP 1997
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for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications.

FILE COVERS 1967 - 5 Sep 1997 VOL 127 ISS 10
FILE LAST UPDATED: 5 Sep 1997 (970905/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

Improved currency of Japanese patents. See HELP JCURR.

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'BI AB' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d l70 1- bib abs hitrn

L70 ANSWER 1 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1997:561815 HCAPLUS
TI Differential inhibition of cytochrome P450 isoforms by the protease inhibitors, **ritonavir**, **saquinavir** and indinavir
AU Eagling, V. A.; Back, D. J.; Barry, M. G.
CS Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, L69 3GE, UK
SO Br. J. Clin. Pharmacol. (1997), 44(2), 190-194
CODEN: BCPHBM; ISSN: 0306-5251
PB Blackwell
DT Journal
LA English
AB To compare the inhibitory potential of the HIV protease inhibitors **saquinavir**, **ritonavir** and indinavir against CYP1A2, CYP2C9, CYP2E1 and CYP3A4 catalyzed metabolic reactions in human liver microsomes in vitro. Microsomes from six human livers were utilized in this study. The probe substrates were phenacetin (CYP1A2), tolbutamide (CYP2C9), chlorzoxazone (CYP2E1) and testosterone (CYP3A4). Metabolites were analyzed by high performance liq. chromatog. IC50 (concn. of inhibitor giving 50% decrease in enzyme activity) and, where appropriate, Ki values were calcd. **Ritonavir** was a very potent inhibitor of CYP3A4 mediated testosterone 6.beta.-hydroxylation (mean Ki=0.019.+-.0.004 .mu.M, mean.+-.s.d.; n=6) and also inhibited tolbutamide hydroxylation (IC50=4.2.+-.1.3 .mu.M, mean.+-.s.d.; n=6). Inhibition of phenacetin O-deethylation and chlorzoxazone 6-hydroxylation was negligible. Indinavir was an order-of-magnitude less potent in inhibiting CYP3A4 (Ki=0.17.+-.0.01 .mu.M) and did not produce appreciable inhibition of the CYP1A2, CYP2C9 or CYP2E1 catalyzed reactions. **Saquinavir** was the least potent CYP3A4 inhibitor (Ki=2.99.+-.0.87 .mu.M) and produced some inhibition of CYP2C9 (approx. 50% at 50 .mu.M). The HIV protease inhibitors have differential effects on CYP isoenzymes. There is obvious potential for clin. significant drug **interactions** particularly with **ritonavir**. Pharmacokinetic drug **interaction** studies are crucial to gain an overall understanding of the beneficial and potentially harmful effects of this important group of drugs.

L70 ANSWER 2 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1997:536450 HCAPLUS
TI Drug **interaction** potential with inhibitors of HIV protease

AU Van Cleef, Gwendolyn F.; Fisher, Evelyn J.; Polk, Ron E.
CS School of Pharmacy, Virginia Commonwealth University/Medical College of Virginia, Richmond, VA, 23298, USA
SO Pharmacotherapy (1997), 17(4), 774-778
CODEN: PHPYDQ; ISSN: 0277-0008
PB Pharmacotherapy Publications
DT Journal
LA English
AB We conducted a retrospective chart review to est. the potential for drug **interactions** in subjects infected with the human immunodeficiency virus-1 when a protease inhibitor was added to existing therapy. Medical records of 50 patients in each of three immunol. strata (CD4 cell counts/.mu.l < 100, 100-199, 200-500) were randomly selected from records of all patients receiving care at the clinic; 114 records were evaluable. The probabilities of one **interaction** or more were 31%, 42%, and 77% of patients if treated with indinavir, **saquinavir**, and **ritonavir**, resp., across all CD4 groups; when the CD4 count was below 100 cells/.mu.l, the probabilities were 55%, 63%, and 93%. Many of these **interactions**, however, resulted from administration of rifabutin, a drug likely to decrease in importance as less toxic alternatives become more widely administered. The potential for drug **interactions** is high when starting protease inhibitor therapy, esp. in patients with low CD4 cell counts who receive **ritonavir**. Concurrent therapy must be evaluated before treatment, as many agents are either contraindicated or require dosage modification.

L70 ANSWER 3 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1997:460198 HCAPLUS
DN 127:116945
TI Protease inhibitors: a therapeutic breakthrough for the treatment of patients with human immunodeficiency virus
AU Lewis, James S., II; Terriff, Colleen M.; Coulston, Daniel R.; Garrison, Mark W.
CS College of Pharmacy, Washington State University, Spokane, WA, USA
SO Clin. Ther. (1997), 19(2), 187-214
CODEN: CLTHDG; ISSN: 0149-2918
PB Excerpta Medica
DT Journal; General Review
LA English
AB A review with 89 refs. As one of the largest growing classes of antiretroviral drugs, protease inhibitors are promising agents for the management of patients infected with the human immunodeficiency virus (HIV). We reviewed the literature and compared efficacy, dosing, side effects, and drug-**interaction** profiles of the protease inhibitors **saquinavir**, **ritonavir**, indinavir, and nelfinavir. We addressed the use of these antiprotease agents as monotherapy vs. use in combination therapy with other antiretroviral medications, and the potential for HIV to develop resistance to this drug class. We also discussed therapy with dual protease inhibitors and the use of protease inhibitors in pregnant or lactating women and in pediatric patients. Finally, we examd. case reports of the addn. of protease inhibitors to an antiretroviral regimen that ultimately decreases or reverses opportunistic infections.

L70 ANSWER 4 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1997:333273 HCAPLUS

DN 127:44485
TI The thiocarboxanilides UC-10 and UC-781 have an additive inhibitory effect against human immunodeficiency virus type 1 reverse transcriptase and replication in cell culture when combined with other antiretroviral drugs
AU Balzarini, J.; De Clercq, E.
CS Rega Inst. Medical Res., Katholieke Univ. Leuven, Louvain, B-3000, Belg.
SO Antiviral Chem. Chemother. (1997), 8(3), 197-204
CODEN: ACCHEH; ISSN: 0956-3202
PB International Medical Press
DT Journal
LA English
AB The thiocarboxanilides represent a structural class of potent and selective human immunodeficiency virus type 1 (HIV-1)-specific reverse transcriptase (RT) inhibitors. Combinations of the clin. candidate thiocarboxanilides UC-10 (oxime ether deriv.) and UC-781 (pentenyloxy ether deriv.) with a variety of nucleoside RT inhibitors (NRTIs) and non-nucleoside RT inhibitors (NNRTIs), two HIV protease inhibitors and one fusion/uncoating inhibitor were evaluated for their inhibitory effects on HIV-1 RT activity and HIV-1 replication in CEM cell cultures. The inhibitory activity of the NNRTIs including UC-10, UC-781, nevirapine, BHAP, .alpha.-APA, 8-chloro-TIBO, MKC-442 and the quinoxaline HBY 097 against HIV-1 RT was highly dependent on the nature of the template/primer used in the HIV-1 RT reaction. However, fractionary inhibitory concn. (FIC) indexes for all drug concns. evaluated in the combination expts. of UC_781 and the other NNRTIs fell within the range 0.5-1.5. This points to a predominantly additive effect of the thiocarboxanilides and other NNRTIs in the inhibition of HIV-1 RT. Similar FIC indexes were obsd. for the combination of UC-781 with the NRTI triphosphates AZT-TP, d4T-TP, ddCTP, ddATP and 3TC-TP and the NRTI diphosphate PMEApp against HIV-1 RT. All these drug combinations showed similar additive inhibitory effects on HIV-1 replication in cell culture. Also, the combinations of UC-10 or UC-781 with the protease inhibitors **Ro31-8959**/008 and ABT 84538.0 and the fusion/uncoating inhibitor bicyclam JM 3100 showed an additive effect (FIC within the 0.5-1.5 range). Thus, irresp. of the nature of the drugs, their combination with the thiocarboxanilides proved merely additive. In no case were antagonistic anti-HIV activity or increased cytotoxicity obsd. In conclusion, thiocarboxanilides combined with a variety of clin. used anti-HIV agents result in additive anti-HIV activity.
IT **127779-20-8**, **Saquinavir 155213-67-5**, **Ritonavir**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(UC-10 and UC-781 have additive inhibitory effect against HIV-1 reverse transcriptase and replication in cell culture when combined with other antiretroviral drugs)

L70 ANSWER 5 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1997:276427 HCAPLUS
DN 126:246812
TI Enhancement of the biological and antiviral activity of HIV protease inhibitors with macrolide and lincosamide antibiotics
IN Schinazi, Raymond F.; Sommadossi, Jean-Pierre
PA University of Alabama at Birmingham, USA; Schinazi, Raymond, F.
SO PCT Int. Appl., 40 pp.

CODEN: PIXXD2
PI WO 9708180 A1 970306
DS UG, W UZ, W VN, W AM, W AZ, W BY, W KG, W KZ, W MD, W RU, W TJ, W TMEE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 96-US13721 960830
PRAI US 95-521474 950830
DT Patent
LA English
AB The cellular uptake of protease inhibitors (e.g. HIV protease inhibitor), in antiviral therapy based on inhibition of a protease required for viral maturation, is diminished by binding of the protease inhibitor to .alpha.1-acid glycoprotein (AAG), an acute-phase protein in serum. This effect is reversed, and the antiviral effectiveness of the protease inhibitors is restored, by **coadministration** of .gtoreq.1 AAG-binding compd., such as a macrolide or lincosamide antibiotic, which has sufficient binding affinity for AAG to competitively bind AAG in the presence of the protease inhibitor. Thus, cellular accumulation of HIV protease inhibitor **SC-52151** by phytohemagglutinin-stimulated human peripheral blood mononuclear cells in the presence of AAG (1 mg/mL) was completely restored (to the level obsd. in the absence of AAG) by addn. of erythromycin to 500 .mu.M.
IT **127779-20-8**, **Ro 31-8959**
143224-34-4, **SC 52151**
147318-81-8, **KNI 272** **155213-67-5**
, ABT 538
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhancement of biol. and antiviral activity of HIV protease inhibitors with macrolide and lincosamide antibiotics)

L70 ANSWER 6 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1997:249706 HCAPLUS
DN 126:287562
TI **Saquinavir** pharmacokinetics alone and in combination with **ritonavir** in HIV-infected patients
AU Merry, Concepta; Barry, Michael G.; Mulcahy, Fiona; Ryan, Mairin; Heavey, Jane; Tjia, John F.; Gibbons, Sara E.; Breckenridge, Alasdair M.; Back, David J.
CS Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, L69 3GE, UK
SO AIDS (London) (1997), 11(4), F29-F33
CODEN: AIDSET; ISSN: 0269-9370
PB Rapid Science Publishers
DT Journal
LA English
AB The most important hepatic enzyme involved in the metab. of protease inhibitors is cytochrome P 450 3A4 (CYP3A4). **Ritonavir** (RIT) is a potent inhibitor of CYP3A4 and inhibits **saquinavir** (SQV) metab. in healthy volunteers. In this study we investigated the kinetics of SQV when administered alone and in combination with RIT in HIV-infected patients. SQV pharmacokinetics were detd. in seven patients who had advanced HIV disease. Steady-state SQV profiles were obtained on two occasions

following treatment with SQV 600 mg three times daily alone and when administered with RIT 300 mg twice daily. Blood samples were obtained at times 0, 1, 2, 4, 6 and 8 h post-dosing. Following centrifugation, sepd. plasma was heated at 58.degree.C for at least 30 min to inactivate HIV and stored at -80.degree.C until anal. using high performance liq. chromatog. For patients treated with SQV alone there was a 12-fold variability in the area under the SQV concn.-time curve (AUC0-8h) ranging from 293 to 3446 ng.cntdot.h/mL. When combined with RIT there was a marked increase in the max. plasma concn. of SQV [median (range), 146 (57-702) vs. 4795 (1420-15810) ng/mL; .apprx.95% confidence interval (Cl), 2988-6819; P = 0.0006, Mann-Whitney U test]. The AUC0-8h for SQV was also significantly increased in the presence of RIT [median (range), 470 (293-3446) vs. 27 458 (7357-108 001) ng.cntdot.h/mL; .apprx.95% Cl, 16 628-35 111; P = 0.0006]. For some patients, administration of SQV 600 mg three times daily results in very low SQV plasma levels and possibly little antiviral effect. Combination of SQV with RIT results in a significant drug **interaction** mediated by enzyme inhibition which exposes patients to very high SQV concns. and potential toxicity. If combination therapy with SQV plus RIT is considered then the dose of SQV should be greatly reduced.

IT **127779-20-8, Saquinavir 155213-67-5, Ritonavir**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**saquinavir** pharmacokinetics alone and in combination with **ritonavir** in HIV-infected human patients)

L70 ANSWER 7 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1997:228825 HCAPLUS
DN 126:301431
TI New drugs - Reports of new drugs recently approved by the FDA: **ritonavir**
AU Ohta, Yukari; Shinkai, Ichiro
CS Banyu Clinical Research, Tokyo, Japan
SO Bioorg. Med. Chem. (1997), 5(3), 461-462
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier
DT Journal
LA English
AB **Ritonavir** (**Norvir, A 84538,** or ABT 538) is a peptidomimetic inhibitor of both HIV-1 and HIV-2 proteases. The concn. of drug that inhibits 50% of viral replication (EC50) ranged from 3.8 to 153 nM depending upon the HIV-1 isolate and the cells employed. The av. EC50 for low passage clin. isolates was 22 nM. In a 1090-patient study, 1.2 g of the drug used **concomitantly** with existing nucleoside therapy, produced a significant decrease in mean viral RNA levels of placebo and an increase in av. change of CD4 count over the first 16 wk. After seven months the mortality rate was 4.8% for **ritonavir** patients and 8.4% for placebo. **Ritonavir** demonstrated additive effects against HIV-1 in combination with either zidovudine (ZDV) or didanosine (ddI). Genotypic anal. of HIV-1 isolates with reduced susceptibility to **ritonavir** showed mutations in the HIV protease gene at amino acid positions 84 (Ile to Val), 82 (Val to Phe), 71 (Ala to Val), and 46 (Met to Ile). Phenotypic and genotypic changes in HIV isolates from selected patients treated with **ritonavir** were monitored in phase I/II trials over a

period of 3-32 wk. Mutation appeared to occur in a stepwise and ordered fashion. The potential for HIV cross-resistance between protease inhibitors has not been fully explored. The abs. bioavailability of **ritonavir** has not been detd. After a 600 mg dose of oral soln., peak concns. of **ritonavir** were achieved approx. 2 and 4 h after dosing under fasting and nonfasting conditions, resp. The isopropylthiazole oxidn. metabolite (M-2) is the major metabolite. Studies utilizing human liver microsome have demonstrated that cytochrome P 450 3A (CYP3A) is the major isoform involved in **ritonavir** metab., although CYP2D6 also contributes to the formation of M-2. Agents that increase CYP3A activity would be expected to increase the clearance of **ritonavir** resulting in decrease of **ritonavir** plasma concn. **Ritonavir** can produce a large increase in plasma concns. of certain highly metabolized drugs. **Ritonavir** prevents fast metab. of **saquinavir** allowing increased blood levels. Addn. of **saquinavir** is not expected to accelerate resistance to **ritonavir** due to the distinct mutation profiles of both drugs. **Norvir** capsules are available for oral administration in a strength of 100 mg **ritonavir**. **Norvir** oral soln. is also available for oral administration as 80 mg/mL of **ritonavir** in a flavored vehicle.

IT **155213-67-5, Ritonavir**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antiviral **ritonavir** as peptidomimetic inhibitor of HIV-1 and HIV-2 proteases)

IT **127779-20-8, Saquinavir**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab., **ritonavir** prevention of; antiviral **ritonavir** as peptidomimetic inhibitor of HIV-1 and HIV-2 proteases)

L70 ANSWER 8 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1997:184660 HCAPLUS
DN 126:166463
TI Use of **ritonavir** (ABT-538) for improving the pharmacokinetics of drugs metabolized by cytochrome P450 in a method of treating aids
IN **Norbeck, Daniel W.**; **Kempf, Dale J.**; Leonard, John M.; Bertz, Richard J.
PA Abbott Laboratories, USA
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
PI WO 9701349 A1 970116
DS W: AU, CA, IS, JP, KR, MX
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 96-US11015 960628
PRAI US 95-654 950629
US 95-3849 950915
DT Patent
LA English
AB A method is disclosed for improving the pharmacokinetics of a drug which is metabolized by cytochrome P 450 monooxygenase by use of

ritonavir. HIV inhibitory action is also claimed by combinations of **ritonavir** with protease inhibitors whose pharmacokinetics are modulated by ritanovir via its inhibitory action on cytochrome P 450.

IT **127779-20-8, Saquinavir 143224-34-4, Sc 52151 147318-81-8, Kni 272**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**ritonavir** inhibits P 450 and modulates drug pharmacokinetics and combined HIV antiviral action with protease inhibitors)

IT **155213-67-5, Ritonavir**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**ritonavir** inhibits P 450 and modulates drug pharmacokinetics and combined HIV antiviral action with protease inhibitors)

L70 ANSWER 9 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1997:156459 HCAPLUS
DN 126:258416
TI Pharmacokinetic enhancement of inhibitors of the human immunodeficiency virus protease by **coadministration** with **ritonavir**
AU **Kempf, Dale J.**; Marsh, Kennan C.; Kumar, Gondi; Rodrigues, A. David; Denissen, Jon F.; McDonald, Edith; Kukulka, Michael J.; Hsu, Ann; Granneman, G. Richard; Baroldi, Paolo A.; Sun, Eugene; Pizzuti, David; Plattner, Jacob J.; **Norbeck, Daniel W.**; Leonard, John M.
CS Dep. Infectious Diseases Res., Abbott Lab., Abbott Park, IL, 60064, USA
SO Antimicrob. Agents Chemother. (1997), 41(3), 654-660
CODEN: AMACCQ; ISSN: 0066-4804
PB American Society for Microbiology
DT Journal
LA English
AB **Coadministration** with the human immunodeficiency virus (HIV) protease inhibitor **ritonavir** was investigated as a method for enhancing the levels of other peptidomimetic HIV protease inhibitors in plasma. In rat and human liver microsomes, **ritonavir** potently inhibited the cytochrome P 450 (CYP)-mediated metab. of **saquinavir**, indinavir, nelfinavir, and VX-478. The structural features of **ritonavir** responsible for CYP binding and inhibition were examd. **Coadministration** of other protease inhibitors with **ritonavir** in rats and dogs produced elevated and sustained plasma drug levels 8 to 12 h after a single dose. Drug exposure in rats was elevated by 8- to 46-fold. A >50-fold enhancement of the concns. of **saquinavir** in plasma was obsd. in humans following a single co-dose of **ritonavir** (600 mg) and **saquinavir** (200 mg). These results indicate that **ritonavir** can favorably alter the pharmacokinetic profiles of other protease inhibitors. Combination regimens of **ritonavir** and other protease inhibitors may thus play a role in the treatment of HIV infection. Because of potentially substantial drug level increases, however, such combinations require further investigation to establish safe regimens for clin. use.

IT **155213-67-5**, A 152184
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(cytochrome P 450 inhibition by; pharmacokinetic enhancement of inhibitors of human immunodeficiency virus protease by **coadministration** with **ritonavir** in relation to metab. by cytochrome P 450)

IT **127779-20-8**, **Saquinavir**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(pharmacokinetic enhancement of inhibitors of human immunodeficiency virus protease by **coadministration** with **ritonavir** in relation to metab. by cytochrome P 450)

L70 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1997:146228 HCAPLUS
DN 126:220162
TI New approaches to using antiretroviral therapy for the management of HIV infection
AU Doran, Cynthia M.
CS Sch. of Pharmacy, Univ. of Wisconsin, Madison, WI, 53706, USA
SO Ann. Pharmacother. (1997), 31(2), 228-236
CODEN: APHRER; ISSN: 1060-0280
PB Harvey Whitney Books Co.
DT Journal; General Review
LA English
AB A review with 51 refs. We aim to review the changes that have occurred in the past 2 yr in the management of HIV infection with antiretroviral agents by contrasting the 1994 with the 1996 Guidelines. Current antiretroviral management strategies include movement away from using zidovudine monotherapy, institution of combination antiretroviral therapy earlier in HIV disease, the use of newer agents such as lamivudine, protease inhibitors (i.e., **saquinavir**, **ritonavir**, indinavir), and nonnucleoside reverse transcriptase inhibitors (i.e., nevirapine, delavirdine), prevention of vertical transmission with zidovudine, and use of HIV-1 RNA detns. (viral load) to guide the initiation and alteration of antiretroviral therapy. These strategies represent a dramatic change from the 1994 Guideline, which recommended zidovudine monotherapy in nonpregnant and pregnant individuals whose CD4 cell counts were less than 500 cells/mm3, when many of the newer agents were not available and the assays to det. viral load were strictly investigational. The difference between the 1994 and 1996 Guidelines is substantial. It is likely that within a year's time, newer information on pathogenesis and antiretroviral agents in development will be known and further management strategies will need to be disseminated. Until then, the International AIDS Society-USA Guidelines for 1996 should be followed as the std. of care.

L70 ANSWER 11 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1997:79291 HCAPLUS
DN 126:165974
TI HIV-1 protease inhibitors, A review for clinicians
AU Deeks, Steven G.; Smith, Mark; Holodniy, Mark; Kahn, James O.
CS University of California, San Francisco, CA, USA
SO JAMA, J. Am. Med. Assoc. (1997), 277(2), 145-153

CODEN: JAMAAP; ISSN: 0098-7484
PB American Medical Association
DT Journal; General Review
LA English
AB A review with .apprx.59 refs. The clin. care of people infected with human immunodeficiency virus (HIV) has been substantially affected by the introduction of HIV-specific protease inhibitors (PIs). The 4 PIs available are **saquinavir** mesylate, **ritonavir**, indinavir sulfate, and nelfinavir mesylate. Comparison studies have not been reported; therefore, an assessment of the available data to aid clinicians and patients in choosing appropriate treatment will be presented. A systematic review of peer-reviewed publications, abstrs. from national and international conferences, and product registration information through Sept. 1996. Criteria used to select studies include their relevance to PIs, having been published in the English language, and pertinence for clinicians. Data quality and validity included the venue of the publication and relevance to clin. care. Oral administration of **ritonavir**, indinavir, or nelfinavir generates sustainable drug serum levels to effectively inhibit the protease enzyme; however, **saquinavir** may not generate sustained levels necessary to inhibit the protease enzyme. Patients treated with **ritonavir**, indinavir, or nelfinavir experience similar redns. in viral load and increases in CD4+ lymphocytes; smaller effects occur among those treated with **saquinavir**. Two randomized placebo-controlled studies conducted among patients with severe immune system suppression and substantial zidovudine treatment experience demonstrated reduced HIV disease progression and reduced mortality with PI treatment. Genotypic resistance to PIs occurs; the clin. relevance of resistance is unclear. The costs of these agents including required monitoring impose new and substantial costs. The PIs have emerged as crit. drugs for people with HIV infection. Optimal use involves combination with reverse transcriptase inhibitors. Resistance develops to each agent, and cross-resistance is likely. These agents must be used at full doses with attention to ensuring patient compliance. The expense of these agents may be offset by forestalling disease progression and death and returning people to productive life. Selecting the initial PI must be individualized, and factors to consider include proven activity, possible toxicities, dosing regimens, drug **interactions**, and costs.

L70 ANSWER 12 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1997:48330 HCAPLUS
DN 126:139333
TI Risks and **synergies** from drug **interactions**
AU Sahai, Jan
CS Clinical Investigation Unit, Ottawa General Hospital, Ottawa, ON, Can.
SO AIDS (London) (1996), 10(Suppl. 1), S21-S25
CODEN: AIDSET; ISSN: 0269-9370
PB Rapid Science Publishers
DT Journal; General Review
LA English
AB A review with .apprx.6 refs. To review what is known from in vitro and in vivo studies about the **interactions**, both potentially beneficial and potentially harmful, of antiretroviral agents with each other and with other classes of drugs. Some **interactions** between nucleoside HIV reverse transcriptase

inhibitors and between nucleoside analogs and HIV protease inhibitors result in greater antiretroviral activity (e.g. zalcitabine with **saquinavir**). Others may increase the risks of toxicity and there are a no. of **combinations** of nucleoside agents with other drugs that should be used with caution or avoided completely. Protease inhibitors are metabolized by cytochrome P 450 CYP3A4 in the liver; because they have the potential to inhibit this enzyme they may **interact** with many other drugs that are metabolized by this pathway. **Ritonavir** also inhibits other cytochrome P 450 enzymes and so **interacts** with numerous drugs from a range of classes. Potentially beneficial **interactions** between protease inhibitors include the increase in **saquinavir** levels brought about by **ritonavir**. Knowledge of additive and **synergistic interactions** between antiretroviral agents should facilitate development of therapeutic regimens with prolonged antiretroviral activity. Thorough investigation of possibly harmful **interactions** with co-administered drugs and education of clinicians and patients about the risks of these **interactions** is required.

L70 ANSWER 13 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1996:693923 HCAPLUS
DN 126:114991
TI Expression, characterization, and mutagenesis of the aspartic proteinase from equine infectious anemia virus
AU Powell, David J.; Bur, Daniel; Wlodawer, Alexander; Gustchina, Alla; Payne, Susan L.; Dunn, Ben M.; Kay, John
CS College Cardiff, Univ. Wales, Cardiff, CF1 3US, UK
SO Eur. J. Biochem. (1996), 241(2), 664-674
CODEN: EJBCAI; ISSN: 0014-2956
PB Springer
DT Journal
LA English
AB The gene encoding the proteinase from equine infectious anemia virus (EIAV) was cloned and expressed in Escherichia coli. The recombinant EIAV proteinase was purified to homogeneity and shown to have the ability to process polyprotein and synthetic peptide substrates of human immunodeficiency virus (HIV) origin with an efficiency that can approach that exhibited by HIV proteinase. EIAV proteinase, however, was not susceptible to inhibition by a wide variety of inhibitors HIV-1 proteinase, including those which have been licensed as anti-AIDS drugs. In this respect, EIAV proteinase behaves like an extreme case of a drug-resistant mutant of HIV-1 proteinase that has arisen under selective drug pressure. Only one potent inhibitor (HBY-793) of HIV-1 proteinase showed comparable efficiency against the EIAV enzyme; the compds. A-77003 and A-76889, which differ only in their stereochem. and which are otherwise structurally identical to HBY-793 from residues P2 to P2' [nomenclature of Schechter, I. & Berger, A. (1967) Biochem. Biophys. Res. Commun. 27, 157-162], were not effective inhibitors of EIAV proteinase. Mutant forms of EIAV proteinase (Thr30.fwdarw.Asp and Ile54.fwdarw.Gly) were generated and their ability to **interact** with substrates and inhibitors was characterized. HBY-793 inhibited [Gly54]proteinase as effectively as the wild-type proteinase but was tenfold less potent against [Asp30]proteinase. Data interpretations are presented, based on the structure solved for the complex between HBY-793 and EIAV [Gly54]proteinase [Gustchina A., Kervinen, J., Powell, D. J., Zdanov, A., Kay, J. &

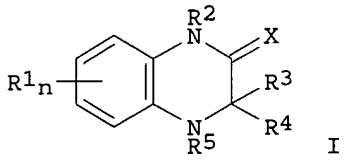
Wlodawer, A. (1996) Protein Sci. 5, 1453-1465].

IT **127779-20-8, RO 31-8959**
147318-81-8, KNI 272 155213-67-5
, ABT 538
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(substrate specificity, susceptibility to HIV proteinase inhibitors , ability to process HIV gag polyprotein, and mutagenesis of recombinant aspartic proteinase from equine infectious anemia virus)

L70 ANSWER 14 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1996:642100 HCAPLUS
DN 125:315866
TI **Ritonavir**
AU Lea, Andrew P.; Faulds, Diana
CS Adis International Limited, Auckland, N. Z.
SO Drugs (1996), 52(4), 541-546
CODEN: DRUGAY; ISSN: 0012-6667
DT Journal; General Review
LA English
AB A review with .apprx.37 refs. **Ritonavir** is a protease inhibitor with an HIV-1 resistance profile similar to that of indinavir, but different from that of **saquinavir**. **Ritonavir** has good oral bioavailability, and may increase the bioavailability of other protease inhibitors including **saquinavir**, nelfinavir, indinavir and VX-478. Clin. significant drug **interactions** have been predicted between **ritonavir** and a range of medications. In patients with HIV-1 infection, **ritonavir** markedly reduced viral load within 2 wk of treatment onset and also increased CD4+ cell counts. In a large placebo-controlled trial in patients with advanced HIV infection, the addn. of **ritonavir** to existing therapy reduced the risk of mortality by 43% and clin. progression by 56% after 6.1 mo. Triple therapy with **ritonavir** plus zidovudine, in combination with lamivudine or zalcitabine, reduced HIV viremia to below detectable levels in most patients with acute, and some patients with advanced HIV infection in 2 small trials. Early results suggest combination therapy with **ritonavir** and **saquinavir** increases CD4+ cell counts and decreases HIV RNA levels in patients with previously untreated HIV infection.
IT **127779-20-8, Saquinavir 155213-67-5, Ritonavir**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(a review of **ritonavir** in humans)

L70 ANSWER 15 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1996:601709 HCAPLUS
DN 125:238651
TI Use of quinoxalines and protease inhibitors in a **composition** for the treatment of AIDS and/or HIV infections
IN Paessens, Arnold; Blunck, Martin; Riess, Guenther; Kleim, Joerg-Peter; Roesner, Manfred
PA Bayer A.-G., Germany
SO Eur. Pat. Appl., 24 pp.
CODEN: EPXXDW
PI EP 728481 A2 960828
DS R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT,

SE
AI EP 96-102129 960214
PRAI DE 95-19506742 950227
DT Patent
LA German
OS MARPAT 125:238651
GI



I

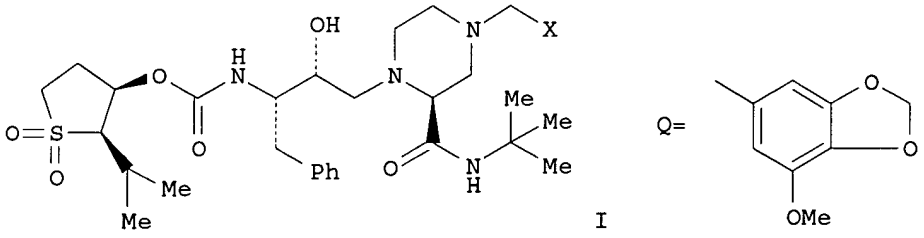
AB **Combinations** of a quinoxaline deriv. [I; R1 = halo, OH, NO2, (substituted) amino, N3, CF3, CF3O, C1-8 alkyl, CN, (substituted) Ph, N-heterocyclyl, etc.; R2, R5 = H, OH, C1-6 alkoxy, aryloxy, C1-6 acyloxy, CN, (substituted) amino, (substituted) C1-8 alkyl, (substituted) C2-8 alkenyl, (substituted) C3-8 alkynyl, (substituted) C3-8 cycloalk(en)yl, etc.; R3, R4 = H, (substituted) C1-8 alkyl, (substituted) C2-8 alkenyl, (substituted) C3-8 cycloalk(en)yl, (substituted)aryl, etc.; or R3R4 or R3R5 complete a (substituted) ring; X = O, S, Se, NR2; n = 0-4] and a peptidomimetic protease inhibitor are useful for treatment of HIV infections and AIDS. Thus, I [R1 = 6-MeO, R2 = R3 = H, R4 = (S)-MeSCH2, R5 = i-PrO2C, X = S] (0.7-6 nM) and **saquinavir** (6-50 nM) **synergistically** inhibited syncytium formation in HIV-infected human lymphocytes in vitro.

IT **127779-20-8, Saquinavir 143224-34-4, SC 52151 147318-81-8, KNI 272 155213-67-5, A 84538**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of quinoxalines and protease inhibitors for treatment of AIDS and HIV infections)

L70 ANSWER 16 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1996:486831 HCAPLUS
DN 125:184502
TI HIV protease inhibitors in early development
AU **Sham, Hing L.**; Chen, Xiaoqi
CS Anti-infective Research Division, Abbott Laboratories, Abbott Park, IL, 60064, USA
SO Expert Opin. Invest. Drugs (1996), 5(8), 977-983
CODEN: EOIDER; ISSN: 0967-8298
DT Journal; General Review
LA English
AB A review with 46 refs. Over the last ten years, two important intervention points in the life cycle of the human immunodeficiency virus (HIV) which involve two viral-specific enzymes, HIV reverse transcriptase (RT) and HIV protease, have been the target of intense research efforts to identify useful therapeutic agents. Several nucleoside analogs which are RT inhibitors have been approved for use in humans. Several nonnucleoside RT inhibitors are now under

development. Within the last twelve months, three different HIV protease inhibitors-**saquinavir**, **ritonavir** and indinavir-have been approved for marketing, thus validating the concept of HIV protease as an important therapeutic target. In this review, several new HIV protease inhibitors that are in early clin. development will be discussed. These compds. are VX-478, AG-1343 (nelfinavir mesylate), palinavir, **KNI-272**, DMP-450, U-103017 and CGP 61755.

L70 ANSWER 17 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1996:367737 HCAPLUS
DN 125:58548
TI Piperazinecarboxamide derivative HIV protease inhibitors useful for the treatment of AIDS
IN Kim, Byeong Moon; Vacca, Joseph P.
PA Merck and Co., Inc., USA
SO Brit. UK Pat. Appl., 53 pp.
CODEN: BAXXDU
PI GB 2292146 A1 960214
AI GB 95-15802 950801
PRAI US 94-289477 940811
DT Patent
LA English
OS MARPAT 125:58548
GI



I

Q=

AB Title compds. I [X = stable 8- to 10-membered bicyclic heterocycle, any ring of which may be satd. or unsatd., and which consists of C atoms and 1-3 heteroatoms selected from N, S, and O, with said heterocycle (un)substituted with OH, halo, C1-4 alkyl, C1-4 alkoxy, or oxo; with proviso that X .noteq. thieno[2,3-b]thien-2-yl or quinolinyl], and pharmaceutically acceptable salts thereof, are useful as HIV protease inhibitors. For example, the preferred compd. I [X = Q] (II) was prepd. in 68% yield by reductive alkylation of the corresponding piperazine deriv. [multi-step prepn. given] with 3-methoxy-4,5-methylenedioxybenzaldehyde and NaBH(OAc3). In a cell-spread assay using MT-4 lymphoid cells infected with wild-type HIV-1, II had CIC95 of 25 nM.

IT **143224-34-4**, Compound E **155213-67-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**synergistic combinations**; prepn. of piperazinecarboxamide derivs. as HIV protease inhibitors)

L70 ANSWER 18 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1996:357017 HCAPLUS
DN 125:26233
TI HIV protease inhibitor **combination**, and therapeutic use

IN Deutsch, Paul J.; Emini, Emilio A.; Vacca, Joseph P.
PA Merck and Co., Inc., USA
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
PI WO 9604913 A1 960222
DS W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, UZ
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-US9956 950807
PRAI US 94-289474 940811
US 94-339369 941114
US 95-492461 950720
DT Patent
LA English
AB The **combination** of the HIV protease inhibitor N-[2(R)-hydroxy-1(S)-indanyl]-2(R)phenylmethyl-4(S)-hydroxy-5-[1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarbamoyl)piperazinyl)]pentaneamide and any one or more of four other potent HIV protease inhibitors is useful in the inhibition of HIV protease, the prevention or treatment of infection by HIV and the treatment of AIDS, either as compds., pharmaceutically acceptable salts, pharmaceutical **compn**. ingredients, whether or not in **combination** with other antivirals, immunomodulators, antibiotics or vaccines. Methods of treating AIDS and methods of preventing or treating infection by HIV are also described.
IT **127779-20-8 143224-34-4 155213-67-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HIV protease inhibitor **combination**, and therapeutic use)

L70 ANSWER 19 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1996:343236 HCAPLUS
DN 125:47999
TI Current knowledge and future prospects for the use of HIV protease inhibitors
AU Moyle, Graeme; Gazzard, Brian
CS Chelsea and Westminster Hospital, Kobler Centre, London, UK
SO Drugs (1996), 51(5), 701-712
CODEN: DRUGAY; ISSN: 0012-6667
DT Journal; General Review
LA English
AB A review with 77 refs. The HIV protease (or proteinase) enzyme is an essential component of the replicative cycle of HIV, performing the post-transitional processing of the gag and gag-pol gene products into the functional core proteins and viral enzymes. Inhibition of this enzyme leads to prodn. of immature noninfectious viral progeny, and hence prevention of further rounds of infection. Structurally, the enzyme is a homodimer consisting of two identical 99 amino acid chains. HIV protease is a member of the aspartic protease family but is structurally dissimilar to human aspartic proteases such as renin, gastricsin and cathepsin D and E, suggesting the possibility of creating inhibitors with a wide therapeutic index. At least 6 inhibitors of HIV protease are currently in clin. development: **saquinavir**, indinavir, **ritonavir**, nelfinavir (AG-1343), **KNI-272** and VX-478, the first four of which have shown antiretroviral activity and acceptable tolerability in initial phase I/II clin.

trials. Resistance or reduced sensitivity to the leading protease inhibitors has been reported in vivo and appears to be assocd. with loss of therapeutic effect. However, resistance patterns appear to be distinct. Treatment for 1 yr with indinavir has been reported to lead to selection of virus in 4 patients, which was cross-resistant to all other leading protease inhibitors. On the other hand, a larger series of clin. isolates from patients receiving **saquinavir** alone or in **combination** with zidovudine for up to 3 yr did not lead to virus cross-resistant to either indinavir or **ritonavir**. This suggests that care should be exercised in designing the sequence of protease usage. Addnl., differing resistance patterns may be used to select **combinations** of protease inhibitors in future trials. Data from studies **combining** protease inhibitors with nucleoside analogs suggest value in terms of larger and more prolonged virol. and immunol. marker responses than are obsd. with single agent therapy, and this is likely to be the primary role for protease inhibitors; both in initial **combinations** for patients commencing therapy and as add-in therapies for patients previously treated with antiretrovirals. However, in vitro and animal pharmacokinetic studies also give evidence of the possibility of **combining** protease inhibitors, potentially leading to improved bioavailability, antiviral **synergy** and delay in emergence of viral resistance.

L70 ANSWER 20 OF 20 HCAPLUS COPYRIGHT 1997 ACS
AN 1996:200484 HCAPLUS
DN 124:277587
TI In vitro antiviral activity of 141W94 (VX-478) in **combination** with other antiretroviral agents
AU Clair, M. H. St.; Millard, J.; Rooney, J.; Tisdale, M.; Parry, N.; Sadler, B. M.; Blum, M. R.; Painter, G.
CS Division of Virology, Glaxo Wellcome Inc., 3030 Cornwallis Rd, Research Triangle Park, USA
SO Antiviral Res. (1996), 29(1), 53-6
CODEN: ARSRDR; ISSN: 0166-3542
DT Journal; General Review
LA English
AB A review, with 9 refs. 141W94 (VX-478) is a novel HIV-1 protease inhibitor with an IC50 of 0.08 .mu.M against HIV-1 (strain IIIB) and a mean IC50 of 0.012 .mu.M against six HIV clin. isolates. 141W94 was **synergistic** on the basis of isobologram anal. with each of the following reverse transcriptase inhibitors: AZT, 935U83, 524W91, 1592U89 and ddI. 141W94 was also **synergistic** with **saquinavir** and additive with either indinavir or **ritonavir**. Resistance to 141W94 has been reported in vitro passage expts. The binding of 141W94 to human .alpha.1-acid glycoprotein was relatively weak (Kd = 4 .mu.M) and the off-rate for the drug is very fast (.gtoreq.100 s-1). Only a 2-fold redn. of in vitro antiviral activity was obsd. in the presence of 45% human plasma. No serious drug assocd. adverse experiences were reported in a Phase I placebo-controlled, single-dose escalation, pharmacokinetic and safety study. The av. concn. of 141W94 at 8 and 12 h after single doses of 900 and 1200 mg, resp., was in excess of 10 times the IC50. As 141W94 is **synergistic** with a variety of anti-HIV-1 agents and exhibits a unique cross resistance profile compared to other protease inhibitors, 141W94 is considered a good candidate for **combination** therapy.

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(FILE 'REGISTRY' ENTERED AT 13:48:06 ON 05 SEP 1997)

FILE 'HCAPLUS' ENTERED AT 13:49:31 ON 05 SEP 1997

FILE 'AIDSLINE' ENTERED AT 13:51:14 ON 05 SEP 1997

L71	0	S	L20
L72	0	S	L21
L73	290	S	RITONAVIR OR NORVIR OR (A OR ABBOTT)()(84538 OR 84 538)
L74	242	S	L28
L75	383	S	SAQUINAVIR OR RO318959 OR RO31 8959 OR RO 31 8959
L76	0	S	L29
L77	21	S	SC52151 OR SC()(52151 OR 52 151)
L78	6	S	L30
L79	6	S	(KNI OR KYNOSTATIN)()227 OR KNI227
L80	32	S	L31
L81	41	S	(KNI OR KYNOSTATIN)()272 OR KNI272
L82	425	S	L74,L75,L77-L81
L83	128	S	L73 AND L82
L84	69	S	L83 AND DRUG THERAPY, COMBINATION/CT

FILE 'AIDSLINE' ENTERED AT 13:57:43 ON 05 SEP 1997

=> d cbib ab 1-

L84 ANSWER 1 OF 69 AIDSLINE
97:19175 Document No.: ICA11-97926906. Treatment of advanced HIV infection with **ritonavir** plus **saquinavir**.
Hirschel B J; Rutschmann O; Fathi M; Gabriel V; Mendoula A; von Overbeck I; Iten A. Divisions of Infectious Diseases, University Hospitals, Geneva, Switzerland. Int Conf AIDS (1996). Vol. 11, Program Supplement, pp. 28 (Abstract No. LB.B.6030). Pub. country: United States. Language: English.

AB Objectives: To conduct a pilot study of the rit/saq combination in advanced HIV infection. Patients: 7 patients with median CD4 count of 10, all with previous AIDS-defining conditions, 5 with active disease (multiple drug-resistant TB with positive blood cultures, microsporidiosis, cryptosporidiosis, MOTT, progressing Kaposi's), and with serious previous adverse effects of nucleoside RT inhibitors, were treated with rit 600 mg b.i.d. from day 1-7. From day 8-14, saq, 200 mg bid was added, increased to 600 mg bid after day 15. Rit was tolerated by all patients; nausea necessitated a transitory decrease in dosage for one. Adding saq did not cause notable side effects; in particular, liver function tests, creatinine, bilirubin did not change. (Table: see text) Conclusions: Rit/Saq was well tolerated by these patients with extremely advanced HIV infections, and produced a marked antiviral effect.

L84 ANSWER 2 OF 69 AIDSLINE
97:19138 Document No.: ICA11-97926869. Combination use of **ritonavir** and **saquinavir** in HIV-infected patients: preliminary safety and activity data. Cameron D W; Sun E; Markowitz M; Farthing C; McMahon D; Poretz D; Cohen C; Follansbee S; Ho D D; Mellors J; Hsu A; Granneman G F; Maki R; Salgo M; Court J; Leonard J. University of Ottawa, ON, Canada. Fax: (613) 737-8682. E-mail:. bcameron@aixl.uottawa.ca.. Int Conf AIDS (1996). Vol. 11, Program Supplement, pp. 20 (Abstract No. Th.B.934). Pub. country: United States. Language: English.
AB Pharmacokinetic synergy and non-overlapping mutational resistance form a compelling basis for **ritonavir-saquinavir** combination treatment. Previous pharmacokinetic studies have demonstrated that the co-administration of the two drugs achieves sustained and high plasma levels of both drugs. To assess the tolerability and antiviral activity of combination regimens, a multicenter, randomized, open-label study of several **ritonavir-saquinavir** dose combinations has been initiated in HIV-infected patients. Entry criteria include CD4 count of 100-500 cells/microliter, no previous exposure to protease inhibitors, and discontinuation of RT inhibitor treatment. Sixty-five patients were randomized to one of two treatment arms: (A) **ritonavir** 400 mg BID + **saquinavir** 400 mg BID or (B) **ritonavir** 600 mg BID + **saquinavir** 400 mg BID. Drugs were initiated in escalating-dose fashion through the first few days of treatment to optimize tolerability. Thirty-three patients have completed two weeks of treatment (15 in treatment arm A, 18 in treatment arm B), and had mean baseline values of 4.63 log(10) HIV RNA particles/ml, 268 CD4 cells/microliter, and 940 CD8/microliter. At two weeks, these patients had a mean decrease in HIV RNA of 1.61 log(10), mean increase in CD4 of 52 cells/microliter, and mean increase in CD8 of 182 cells/microliter. Changes in the two treatment assignments were comparable. Both regimens have been generally well-tolerated. Two of 65 patients (3%) have discontinued from the study. Mild circumoral paresthesia, diarrhea, and nausea were the most frequently reported adverse events and were generally transient. Elevations of serum triglycerides have also been observed. Additional data following six weeks of treatment with these regimens will be presented.

L84 ANSWER 3 OF 69 AIDSLINE
97:18517 Document No.: MED-97288678. Side-effects of **ritonavir** and its combination with **saquinavir** with special regard to renal function [letter]. Witzke O; Plentz A; Schafers R F; Reinhardt W; Heemann U; Philipp T. AIDS (1997). Vol. 11, No. 6, pp. 836-8. Journal code: AID. ISSN: 0269-9370. Pub. country: United States. Language: English.

L84 ANSWER 4 OF 69 AIDSLINE
97:18167 Document No.: MED-97239094. **Saquinavir** pharmacokinetics alone and in combination with **ritonavir** in HIV-infected patients. Merry C; Barry M G; Mulcahy F; Ryan M; Heavey J; Tjia J F; Gibbons S E; Breckenridge A M; Back D J. Department of Pharmacology and Therapeutics, University of Liverpool, UK. AIDS (1997). Vol. 11, No. 4, pp. F29-33. Journal code: AID. ISSN: 0269-9370. Pub. country: United States. Language: English.
AB OBJECTIVE: The most important hepatic enzyme involved in the

metabolism of protease inhibitors is cytochrome P450 3A4 (CYP3A4). **Ritonavir** (RIT) is a potent inhibitor of CYP3A4 and inhibits **saquinavir** (SQV) metabolism in healthy volunteers. In this study we investigated the kinetics of SQV when administered alone and in combination with RIT in HIV-infected patients. DESIGN: SQV pharmacokinetics were determined in seven patients who had advanced HIV disease. Steady-state SQV profiles were obtained on two occasions following treatment with SQV 600 mg three times daily alone and when administered with RIT 300 mg twice daily. METHODS: Blood samples were obtained at times 0, 1, 2, 4, 6 and 8 h post-dosing. Following centrifugation, separated plasma was heated at 58 degrees C for at least 30 min to inactivate HIV and stored at -80 degrees C until analysis using high performance liquid chromatography. RESULTS: For patients treated with SQV alone there was a 12-fold variability in the area under the SQV concentration-time curve (AUC0-8h) ranging from 293 to 3446 ng.h/ml. When combined with RIT there was a marked increase in the maximum plasma concentration of SQV [median (range), 146 (57-702) versus 4795 (1420-15810) ng/ml; approximately 95% confidence interval (CI), 2988-6819; P = 0.0006, Mann-Whitney U test]. The AUC0-8h for SQV was also significantly increased in the presence of RIT [median (range), 470 (29-3446) versus 27,458 (7357-108,001) ng.h/ml; approximately 95% CI, 16,628-35,111; P = 0.0006]. CONCLUSIONS: For some patients, administration of SQV 600 mg three times daily results in very low SQV plasma levels and possibly little antiviral effect. Combination of SQV with RIT results in a significant drug interaction mediated by enzyme inhibition which exposes patients to very high SQV concentrations and potential toxicity. If combination therapy with SQV plus RIT is considered then the dose of SQV should be greatly reduced.

L84 ANSWER 5 OF 69 AIDSLINE

97:17982 Document No.: AIDS-97702580. [ABC of the antivirals] Project Inform]. ABC de los antivirales. Anonymous. Sidahora (1996). pp. 19-32. Pub. country: United States. Language: Spanish.

AB Scientists have tried to inhibit or slow down the HIV virus ever since the virus was identified as the cause of AIDS. Although the efforts have not produced a long-term solution, significant progress has been made. There is a correlation between the increase in HIV levels and the advanced state of the disease. Antiviral therapies are discussed, including when to start the treatment, what drugs to use, and how to find out if the treatment is working. Some of the drugs seem to stop the replication of the HIV virus; however, they do not eradicate the virus. AZT (zidovudine/Retrovir), ddI (didadosine/Videx), ddC (zalcitabine/Hivid), d4T (stavudine/Zerit) and 3TC (lamivudine/Epivir) are some of the most common drugs on the market today. Information on research, side effects, doses, interactions with other drugs, and where to get these drugs is provided. Protease inhibitors, another type of drug, include **saquinavir**, **ritonavir** and indinavir (Crixivan).
Much research has been done with these drugs, however, they are very difficult to produce. The combination of AZT and 3TC have shown positive results, and the future of antiviral therapies seems to be heading toward combination therapy.

L84 ANSWER 6 OF 69 AIDSLINE

97:17956 Document No.: AIDS-97702554. ICAAC update. Coppedge B. STEP Perspect (1996). Vol. 8, No. 3, pp. 15-6. Pub. country: United States. Language: English.

AB Research topics presented at the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) are highlighted. Topics include the clinical benefits of 3TC (lamivudine), combination **ritonavir/saquinavir** therapy, and results of an initial study of a new protease inhibitor, 141W94, under development by Glaxo Wellcome.

L84 ANSWER 7 OF 69 AIDSLINE

97:17307 Document No.: MED-97307105. Cytomegalovirus retinitis after initiation of highly active antiretroviral therapy. Jacobson M A; Zegans M; Pavan P R; O'Donnell J J; Sattler F; Rao N; Owens S; Pollard R. Department of Medicine, University of California, San Francisco 94110, USA. mjacobson@sfaids.ucsf.edu. LANCET (1997). Vol. 349, No. 9063, pp. 1443-5. Journal code: L0S. ISSN: 0140-6736. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: In previous natural history studies and clinical trials, AIDS-related cytomegalovirus (CMV) retinitis has occurred primarily in patients with absolute CD4 counts of 50 cells/microL or less (0.05 x 10(9)/L) at the time of diagnosis. METHODS: We report five patients identified from our clinical practices who were diagnosed with CMV retinitis while their CD4 counts were above 195 cells/microL. We also analysed, based on CD4 counts, 76 AIDS patients with newly diagnosed CMV retinitis whose CD4 lymphocyte enumerations were done in laboratories that maintained certification in a common external quality control programme. FINDINGS: 5-24 weeks before retinitis was diagnosed, all five patients had had absolute CD4 lymphocyte counts of less than 85 cells/microL, and 4-7 weeks before diagnosis, all five patients had started taking highly active antiretroviral treatment (HAART) regimens. Only one (4%) of 27 patients enrolled in the trial between July, 1995, and February, 1996, had an absolute CD4 count of more than 50 cells/microL, and none of 27 had an absolute CD4 count of more than 100/microL on entry to the trial. However, from March, 1996 (when indinavir and **ritonavir** were approved by the FDA for marketing in the USA), to August, 1996, 14 (29%) of 49 patients had CD4 counts of more than 50/microL and seven (14%) of 49 had a CD4 count of more than 100 cells/microL on entry. INTERPRETATION: These findings suggest that the early immunological effects of HAART may not provide sufficient protection to prevent CMV retinitis in patients who have very low CD4 counts when therapy is started. Clinicians should note that CMV retinitis may now occur in patients who have CD4 counts of more than 100 cells/microL.

L84 ANSWER 8 OF 69 AIDSLINE

97:17193 Document No.: MED-97297092. Protease inhibitors: a therapeutic breakthrough for the treatment of patients with human immunodeficiency virus. Lewis J S 2nd; Terriff C M; Coulston D R; Garrison M W. Washington State University, College of Pharmacy, Spokane, USA. CLINICAL THERAPEUTICS (1997). Vol. 19, No. 2, pp. 187-214. Journal code: CPE. ISSN: 0149-2918. Pub. country: United States. Language: English.

AB As one of the largest growing classes of antiretroviral drugs, protease inhibitors are promising agents for the management of patients infected with the human immunodeficiency virus (HIV). We reviewed the literature and compared efficacy, dosing, side effects, and drug-interaction profiles of the protease inhibitors **saquinavir**, **ritonavir**, indinavir, and nelfinavir. We addressed the use of these antiprotease agents as monotherapy versus use in combination therapy with other antiretroviral

medications, and the potential for HIV to develop resistance to this drug class. We also discussed therapy with dual protease inhibitors and the use of protease inhibitors in pregnant or lactating women and in pediatric patients. Finally, we examined case reports of the addition of protease inhibitors to an antiretroviral regimen that ultimately decreases or reverses opportunistic infections.

L84 ANSWER 9 OF 69 AIDSLINE

97:16615 Document No.: AIDS-97926815. Mutations associated with reduced sensitivity to **saquinavir** occur in a minority of patients treated in combination with ddC: results from a phase III clinical trial (NV14256). Race E; Sheldon J G; Kaye S; Gilbert S M; Moffatt A R; Duncan I B. Roche Research Centre, Welwyn Garden City, U.K. 4th Conf Retro and Opportun Infect (1997). pp. 175 (Abstract No. 600). Pub. country: United States. Language: English.

AB After full sequencing to detect all patterns of change in the HIV proteinase gene during **saquinavir** (SQV) treatment, it has been established that two mutations (48V and 90M) are key to the development of reduced sensitivity to the drug. This signature differs from other PIs. In contrast to many of the mutations associated with resistance to indinavir (eg 46I, 71V, 82I/F), 48V and 90M have never been seen in samples from untreated patients, and are therefore a reliable index of reduced sensitivity to SQV in vivo. In phase I/II clinical trials of SQV, substitutions at codons 48 or 90 were detected in around 40% of patients after 1 year of treatment. The double mutation was rare, occurring in only 6% of patients treated with SQV alone and in none who received SQV in combination with reverse transcriptase inhibitors. NV14256 is a randomised, double blind comparison of SQV (600mg tid), ddC (HIVID, 0.75mg tid) and the combination. Clinical end point analysis of this trial has shown a significant clinical benefit of SQV and ddC over ddC alone, with respect to both time to AIDS defining events (reduced by 53%, p=0.0002) and survival (increased by 71%, p=0.002). The full HIV protease sequence was analysed in pre- and post-treatment plasma samples from 24 patients treated with SQV alone and 27 patients treated with SQV and ddC. In the monotherapy arm the codon change L90M was selected for and changes at positions 10, 63 and 71 were enhanced. In the combination therapy arm the only significant change observed was at L90M. Comparison of genotypic and phenotypic data showed that only 48V and 90M correlated with reduced sensitivity to SQV, endorsing their use as resistance markers. In post-treatment plasmas 10I, 63Q/T/P and/or 71T/V were found to be significantly associated with a mutation at codon 90, and may perform a supporting function. However, the presence of the same amino acids at these positions in pre-treatment plasma did not predict the development of 90M. The proteinase substitution 90M was detected in the plasma of only 3/14 (21%) of patients after greater than 40 weeks of treatment with SQV in combination with ddC, and the 48V mutation occurred in only 1/16 (6%) samples at 24 weeks and in 0/14 at greater than 40 weeks post-treatment. The emergence of reduced sensitivity to SQV in the clinic is likely to be further suppressed by drug combinations which will maintain viral load below the level of detection (eg Triple combinations or SQV+ **ritonavir**).

L84 ANSWER 10 OF 69 AIDSLINE

97:16349 Document No.: AIDS-97926549. Indinavir (I), **saquinavir** (S), **ritonavir** (R): a comparative trial. Mars M E; Loi S; Suzan V; Gallais H. Infectious Diseases Unit, la Conception,

Marseille, France. 4th Conf Retro and Opportun Infect (1997). pp. 101 (Abstract No. 198). Pub. country: United States. Language: English.

AB OBJECTIVE : To compare the efficacy and tolerance of the 3 antiprotease inhibitors in combination with 2 antiretroviral drugs, in HIV infected patients. PATIENTS AND METHODS : Between April 1st 1996, and October 1st 1996, 313 HIV+ patients were enrolled in an open label trial aimed at comparing the efficacy and tolerance of I., S. and R.. I. was added to the bitherapy in 98 patients (group I), S. in 165 patients (group S), and R. in 50 patients (group R). The 3 groups were comparable (age, sex, HIV history, initial CD4 count and initial viral load). We have analysed the major criterion: mortality, and the minor ones: appearance of an opportunistic infection, quality of life (QOL), tolerance, viral load and CD4 evolution. RESULTS: We noted no difference with respect to mortality and appearance of an opportunistic infection. In group I, we observed more improvements of QOL (55% p=0.0003), and more decreases of initial viral load to an undetectable value (p=0.002). In group R we noted more adverse events (p=0.00000001). Concerning CD4 cells count evolution, we observed a lower rate of increases in group S (p=0.027), and a more important increase in group R. (191 plus or minus 98.2/mm3, p=0,04). In addition, we noted that the efficacy of a protease inhibitor is more important when the initial viral load is higher than 100 000/ml (p=0.01) and when the initial CD4 count is lower than 50/mm3 (p=0.04). DISCUSSION AND CONCLUSIONS : In 1996, 3 protease inhibitors are allowed in France, and the choice is difficult for the clinician. Our study tends to prove that Indinavir, a well-tolerated drug, leads to more improvements of QOL and more viral loads lower than 200/ml, its improvement of initial CD4 cells count is less important than R. one, but R. has often a bad tolerance.

L84 ANSWER 11 OF 69 AIDSLINE

97:16334 Document No.: AIDS-97926534. Genotypic analysis of HIV-1 variants isolated from patients treated with the protease inhibitor nelfinavir, alone or in combination with d4T or AZT and 3TC. Patick A K; Duran M; Cao Y; Ho T; Zhou P; Keller M R; Chapman S; Anderson R; Kuritzkes D; Shugarts D; Ho D; Markowitz M. Agouron Pharmaceuticals, Inc., La Jolla, CA. 4th Conf Retro and Opportun Infect (1997). pp. 66 (Abstract No. 10). Pub. country: United States. Language: English.

AB Nelfinavir (formerly AG1343) is a selective, nonpeptidic inhibitor of HIV protease discovered using protein structure-based drug design methodologies. Sequence analysis of protease genes obtained by RT-PCR from plasma vRNA from patients from Pilot Phase II monotherapy, dose range-finding studies identified as the predominant mutation, a previously undescribed change from an aspartic acid (D) to an asparagine (N) at position 30. Protease genes from patient isolates containing the D30N change were further analyzed for additional mutations occurring over time. Results indicate that the D30N mutation was stably maintained up to 44 weeks of study. The appearance of D30N was occasionally associated with concurrent or sequential emergence of other changes including M36I, M46I, A71T, V and N88D,S. Mutations described for other protease inhibitors were never observed (G48V, V82F/T, I84V) or only rarely observed (L90M) in all patients studied (n=55). Sequence analysis of protease genes isolated from patients treated with nelfinavir in combination with d4T also revealed the occurrence of D30N. In phenotype assays, clinical isolates which exhibited a reduction in

susceptibility to nelfinavir contained the D30N change while isolates which lacked this mutation were susceptible to nelfinavir. Moreover, HIV variants with high-level resistance to nelfinavir were fully susceptible to indinavir, **saquinavir**, **ritonavir**, and VX-478. This data suggests the pathway to resistance to nelfinavir is unique and mediated through D30N and that subsequent treatment with other protease inhibitors may be effective. Sequence analysis of protease genes from patients from ongoing Phase III clinical trials of nelfinavir alone or in combination with AZT and 3TC is currently underway.

L84 ANSWER 12 OF 69 AIDSLINE

97:16333 Document No.: AIDS-97926533. Pharmacokinetics/pharmacodynamics of **ritonavir-saquinavir** combination therapy.
Granneman G R; Hsu A; Sun E; Leonard J M; Xu Y; Rode R. Abbott Laboratories, Abbott Park, IL. 4th Conf Retro and Opportun Infect (1997). pp. 177 (Abstract No. 609). Pub. country: United States. Language: English.

AB Interim results from a dose-ranging study of the efficacy of **ritonavir** (R) and **saquinavir** (S) combinations have been assessed in regard to the magnitude of the pharmacokinetic (PK) interaction, and anti-HIV pharmacodynamic (PD) effect. Dosage (mg) groups are: A) 400 R, 400 S q12h, B) 600 R, 400 S q12h, C) 400 R, 400 S q8h, and D) 600 R, 600 S q12h. Groups A and B have completed 16 weeks of treatment. Median HIV RNA production was profoundly suppressed in a biphasic manner, declining from [approx]10(5) copies/mL to the limit of quantitation by Week 9. Median half-lives for the two phases were 2 and 13 days, respectively. Increases in CD4+ cells, typically greater than 100/microliter, were fitted to a first-order model, with an estimated half-life of [approx] 8 days. Various explanatory variables were investigated as predictors of response. Although duration of infection did not affect the attainment of nondetectable RNA levels, it was associated with slower decreases in RNA and smaller increases in absolute numbers of CD4 cells. Previous AZT therapy was also associated with smaller increase of CD4 cells. RNA and CD4 responses were poorly correlated with R and S levels, since conc>>EC(50)s. Median RNA and CD4 data were also simultaneously fitted with a variety of simple PK/PD models of viral dynamics for Groups A and B. The biphasic decline in RNA was consistent with models that assumed at least two pools of infected cells (with different lifespans) or one pool of infected cells in a distribution equilibrium (e.g., between RNA+/- states, or plasma/lymphatic). The models took into account the time course of R and S exposure, based on typical clearances for the groups. The effect of the two agents on HIV protease for wildtype virus was based on a competitive inhibitory E(max) model with R and S protein-corrected in vitro EC(50)s of 1.07 and 0.087 microgram/mL, with Hill coefficients of 2.28 and 1.02, respectively.

L84 ANSWER 13 OF 69 AIDSLINE

97:16327 Document No.: AIDS-97926527. The use of antiretroviral therapy in association with evolving standards of practice. Bozek P S; Weidle P J; Perdue B E; Everson R E. Adult HIV Program, University of Maryland Medical System, Baltimore, MD. 4th Conf Retro and Opportun Infect (1997). pp. 111 (Abstract No. 257). Pub. country: United States. Language: English.

AB Objective: To describe the changes in the use of antiretroviral therapy (ART) before and after the acceptance of combination ART (CoT) and the publication of the 1996 ART treatment recommendations.

Methods: A cohort of patients (pts) from a university based inner city HIV clinic were randomly selected for tracking of ART. ART data was collected by chart review from a single visit during each of 4 time periods. Chosen time periods correspond with landmark changes in HIV therapy. Periods defined as Period 1 (monotherapy), Period 2 (CoT & introduction of lamivudine and **saquinavir**), Period 3 (clinical benefit of protease inhibitors, approval of **ritonavir** and indinavir), and Period 4 (new consensus guidelines for HIV therapy). Information included use of any ART, CoT, protease inhibitor (PI), the number of antiretroviral drugs (#), and mean cost of ART/month (cost/mo). Results: The percentage of pts on any ART for each period were as follows 1: 63%, 2: 56%, 3: 75%, 4: 77%. Data provided in table is for those pts on ART. (Table: see text) Multivariate analysis of period 4 revealed only risk factor for HIV infection was associated with PI use. Those with risk factor of injection drug use received PI less often than those with risk factor of heterosexual or homosexual contact (20%, 63%, 71%, respectively). Conclusions: The proportion of pts on ART remained constant over the time periods examined. However, the use of CoT increased more than 10 fold. PI are now used in approximately one-half of all pts. However, injection drug users are prescribed PI less than other pts. The number of prescribed ART and cost per month increased with each time period. This correlates with the increaseing trends of CoT and PI use. New information and the introduction of new agents has changed the way ART are being prescribed at this clinic in accordance with recommendations and evolving standards of practice.

L84 ANSWER 14 OF 69 AIDSLINE

97:16304 Document No.: AIDS-97926504. "Salvage therapy" using the combination of **ritonavir** and **saquinavir** in patients with advanced HIV infection. Steinhart C R; George S A; Mann R D. Mercy Hospital Special Immunology Services, Miami, FL. 4th Conf Retro and Opportun Infect (1997). pp. 101 (Abstract No. 199). Pub. country: United States. Language: English.

AB Objective: to determine the safety and possible efficacy of combination protease inhibitor therapy with 2 nucleoside analogs in subjects intolerant to **ritonavir**. Methods: subjects with CD4 counts less than or equal to 100/mm3 not responding to combination therapy with 2 nucleoside analogs, and not able to tolerate **ritonavir** at the standard dose of 600 mg po bid were enrolled in an open-label trial. Subjects were continued on their current double-nucleoside therapy and given the combination of **saquinavir**, 800 mg po bid, and **ritonavir**, 400 mg po bid. Hematogical and biochemical measurements, plasma HIV RNA by RT-PCR, and CD4 lymphocyte counts were obtained at baseline and every 4 weeks during treatment. Results: To date, 8 subjects have been followed for 2-5 months. CD4 counts have increased in 7/8 subjects from a mean baseline value of 52 plus or minus 7 cells/mm3 to 152 plus or minus 25/mm3 at 3 months. Viral load has decreased from a mean baseline of 81,750 (4.65 log(10)) copies/ml to undetectable levels in 6/8 subjects. Mean reduction in viral load has been 1.71 log(10) copies/ml. All subjects have tolerated the combination well without any clinically significant changes in laboratory values. Conclusions: Combination antiretroviral therapy with 2 nucleosides and the protease inhibitors **saquinavir** and **ritonavir** in subjects with advanced HIV infection intolerant to the recommended dose of **ritonavir** leads to a reduction in plasma HIV RNA and an increase in CD4 count that that

are sustained for greater than or equal to 3 months and is well-tolerated. Controlled trials of the 4-drug regimen are indicated to determine the long-term safety and efficacy of this combination in subjects with advanced HIV infection.

L84 ANSWER 15 OF 69 AIDSLINE

97:16263 Document No.: AIDS-97926463. Efficacy and safety of quadruple combination therapy in treatment experienced HIV/AIDS patient. Barbour CO I I. Desert AIDS Project, Palm Springs, CA. Fax: (619) 323-1539. 4th Conf Retro and Opportun Infect (1997). pp. 109 (Abstract No. 245). Pub. country: United States. Language: English.

AB Objective: To evaluate the safety and efficacy of combination therapy with **Norvir** (**Ritonavir**)+ Invirase (**Saquinavir**)+ two nucleoside reverse transcriptase inhibitors. Patient Population: 32 HIV infected patients with CD4 cell counts less than 250. All patients had HIV viral loads greater than 5000 or evidence of disease progression, despite 4 months of triple drug therapy (2 nucleoside reverse transcriptase inhibitors and 1 protease inhibitor). Regimen: Combination of **Norvir** 600mg. BID + Invirase 400mg. BID, and two nucleoside reverse transcriptase inhibitors. Assessment: Safety monitoring was performed throughout the study with baseline labs and at weeks 2, 4, 8, 12, and 16. Viral RNA-PCR measurements and CD4 cell counts were obtained at baseline, and weeks 4, 8, 12, and 16. Results: The study enrolled 32 patients of which 2 were withdrawn secondary to adverse side effects. The mean CD4 cell count at baseline was 79 cells/mm3 (Range 9-236), and mean HIV-RNA viral load was 4.86 log(10) copies/ml (Range 3.29 -5.82). At the 4 week point 53% of patients had achieved a reduction of HIV-RNA viral load below the limits of detection at 400 copies/ml. The 8 and 12 week data revealed that 96.6% of patients had a viral load below the limits of detection. The mean increase in CD4 cell count was 42 cells/mm3 at 4 weeks, 64 cells/mm3 at 8 weeks, and 72 cells/mm3 at 12 weeks. Conclusion: Evaluation of the data reveals the combination of **Norvir** and Invirase with 2 nucleoside reverse transcriptase inhibitors to be safe in the majority of patients, and effective in reducing HIV-RNA in patients with extensive prior use of antiretrovirals. The mean change in viral load of -2.26 log(10) and mean rise in CD4 cell count of 72 cells/mm3 were observed at 12 weeks.

L84 ANSWER 16 OF 69 AIDSLINE

97:16252 Document No.: AIDS-97926452. Prevalence of protease inhibitor (PRI) and reverse transcriptase inhibitor (RTI) drug-resistance mutations in a rural Iowa HIV+- population: implication for treatment. Kozal M; Leahy N; Ross J; Swack N; Stapleton J. University of Iowa, Iowa City, IA. 4th Conf Retro and Opportun Infect (1997). pp. 66 (Abstract No. 9). Pub. country: United States. Language: English.

AB Objective: To determine the prevalence of PRI and RTI drug-resistant mutations & polymorphisms (polys) in a rural HIV-infected population and to investigate the effect preexisting mutations & polys within PR gene have on the frequency, rapidity and patterns of emergence of PR mutations in HIV+ patients in relation to patients beginning PRI therapy without any PRI resistance mutations. Design/Measurements: Retrospective, cross-sectional analysis of viral isolates, and a prospective, observational, longitudinal analysis of Pol gene sequences from patients who were drug naive or RTI experienced and were changed to an alternate Rx (including **Saquinavir**, Indinavir or **Ritonavir**). All Pol genes were sequenced

using both automated sequencing (ABI) and DNAChips (Affymetrix) using methods previously published (Kozal et.al Nature Med 1996, 2:753). Results: Pol genes from HIV-1 isolates from 72 PRI-naive patients were sequenced. Mutations known to confer resistance to all 3 licensed PRIs were identified. 26% of patients had changes within the PR gene associated with PRI resistance, specifically at codons 10/20/24/45/54/63/71/82. 21% of patients harbored viruses with multiple PR mutations. 25% of patients contained RTI drug-resistant mutations (58% AZT, 17% 3TC, 25% ddN). Of newly Dx HIV- infected patients (n=60) 3% harbored RTI-resistant mutations. Longitudinal results from patients with and without PRI mutations at the start of RTI+PRI therapy will be presented. Conclusion: PRI mutations associated with PRI drug-resistance were prevalent in this rural PRI-naive patient cohort. RTI drug-resistant mutations were also prevalent in patients both RTI-naive newly Dx and RTI-experienced. The high frequency with which drug-resistance mutations occur suggests that Rx based on blind algorithms of drug switching may lead to patients being switched or started on Rx regimens for which their HIV-1 isolates are already resistant.

L84 ANSWER 17 OF 69 AIDSLINE

97:16246 Document No.: AIDS-97926446. Antiretroviral prescribing patterns following introduction of protease inhibitors (PI). Coleman R L; Brosgart C L; Mitchell T F; Dyner T; Gee L; Abrams D I. University of California, San Francisco, CA. 4th Conf Retro and Opportun Infect (1997). pp. 112 (Abstract No. 258). Pub. country: United States. Language: English.

AB Purpose: A new class of antiretrovirals, protease inhibitors (PI), was introduced in the first half of 1996. To determine the extent to which providers have incorporated these drugs into their patterns of care we conducted a national survey of preferred antiretroviral regimens. Methods: We surveyed 1166 providers in over 20 US cities between June and July 1996 using a self-administered questionaire. Respondents were asked to indicate the regimen(s) they usually prescribed as first-line therapy for patients in the following groups; CD4 cell count greater than 500, 200-500, 50-200 and less than 50. Results: 167 surveys were undeliverable. We received 524 responses. 179 respondents were no longer in clinical practice or did not see HIV patients, leaving 345 evaluable surveys (42% response rate). The most common response for the greater than 500 group was no therapy (69%) followed by nucleoside combination; for the 200-500 group, AZT/3TC (20%); for the 50-200 group, split evenly between AZT/3TC and indinavir/nucleoside(s) combination; and for the less than 50 group, PI/nucleoside(s) combination. Within each group, the nucleoside combinations most commonly preferred were AZT/3TC followed by d4T/3TC, AZT/ddI and AZT/ddC. The PI/nucleoside(s) combination of choice most often included indinavir, followed by **ritonavir**, then **saquinavir**. Conclusions: Providers indicated that they used more aggressive antiretroviral therapy for more advanced HIV disease. The specific nucleoside combination and PI/nucleoside(s) combination most favored did not vary across different stages of disease.

L84 ANSWER 18 OF 69 AIDSLINE

97:16242 Document No.: AIDS-97926442. Kaplan-Meier analysis of interruption probability of a protease inhibitor, **saquinavir** (S), indinavir (I) or **ritonavir** (R) in 177 patients receiving a combination of protease inhibitors and reverse transcriptase inhibitors (IRT). Valette M; Gerard Y; Ajana F; Bocket

L; de la Tribonniere X; Bourez J M; Mouton Y. Service Regional Univ. de Maladies Infectieuses, Tourcoing, France. 4th Conf Retro and Opportun Infect (1997). pp. 101 (Abstract No. 197). Pub. country: United States. Language: English.

AB In the reference center of AIDS of the North of France, we performed a retrospective study designed to compare the probability of pursuit of the protease inhibitors; from Feb 20th 1996 to Oct 6th 1996. 177 patients received for the first time a protease inhibitor, defining 3 groups of treatment. The comparability of the treatment groups was assessed with respect to covariates as: classification CDC, CD4+ rate and viral load (V.L) value, and the combining of IRT with Protease inhibitors. (Table: see text) The rate of interruption was 4 times higher in S group than in the I group (relative risk: RR= 4,4); p is less than 0,01 by log-rank test of Kaplan-Meier curves, from 1.5 month on. This rate was 2.8 times higher in R group than in I group all along during the whole period (p is less than 0,001). There was no significant difference between the S group and the R group. Therefore, within the limits of this study, I seems more interesting than S and R in terms of probability pursuit of treatment because of better efficiency and fewer adverse effects.

L84 ANSWER 19 OF 69 AIDSLINE

97:16227 Document No.: AIDS-97926427. Further reduction in plasma HIV load in patients with advanced AIDS when a second protease inhibitor was added to triple drug combination therapy. Berger D S; Bucher G; Delaney K; Wittert H; Gomatos P. Chicago Center for Special Immunology, Chicago, IL. 4th Conf Retro and Opportun Infect (1997). pp. 109 (Abstract No. 244). Pub. country: United States. Language: English.

AB Objective: To assess the effect in patients (PTS) with advanced AIDS of quadruple antiretroviral therapy, specifically the additional effect of a second protease inhibitor (PI) on triple drug combination therapy. Methods: In a retrospective analysis of 18 PTS with advanced AIDS we determined the efficacy during three periods of combination drug therapy. During period 1, all individuals had been taking long-standing combination reverse transcriptase inhibitor (RTI) drug therapy. During period 2, **ritonavir** (RTV) 800 or 1200 mg qd or **saquinavir** (SQV) 400 or 800 mg qd was added to the combination RTI's. During period 3, all individuals were taking RTV and SQV in addition to combination RTI's. Log(10) changes in plasma HIV loads are reported. Results: All 18 PTS were gay males. Mean time since HIV dx was 9.0 yrs and since AIDS dx was 4.1 years. 34% had CMV end-organ disease and 34% had a history of wasting. One PT withdrew with diarrhea due to dual PI therapy and was dropped from period 3 analysis. At baseline, end of period 1, mean values were as follows: RTI use, 4.4 yrs; CD4 cell count was 65 (2-202), plasma HIV load was 5.21 log(10). Mean duration of single PI therapy (period 2) was greater than 5 months. By the end of the period 2 (2RTI + 1PI) CD4 cell count increased to a mean of 101 (5-354); and mean viral load decreased 0.76 log(10), to 4.45 log(10). To date, mean time on two RTIs and dual PIs (Period 3) was 6 months. Mean CD4 cell count increased further to 163 (6-495). An additional .85 log(10) mean decrease occurred in plasma HIV load during dual PI therapy, to a mean of 3.60 log(10) (2.70-4.38). The overall mean viral load decrease from baseline was at least 1.61 log(10). The mean ANC's after Periods 1,2,3 were 1894, 2702 and 4239; mean Hct's were 38.2, 39.8 and 39.6. Conclusion: Addition of a second PI (dual PI therapy RTV/SQV), was well tolerated and resulted in additional increases in CD4 cell count and

further reduction in plasma HIV load in 82% of PTS with advanced AIDS and history of long-standing combination RTI therapy. During PI therapy there was concomitant improvement in ANC and Hct.

L84 ANSWER 20 OF 69 AIDSLINE

97:16226 Document No.: AIDS-97926426. The use of protease inhibitors in the community program for clinical research on AIDS (CPCRA). Baxter J D; Neaton J; Wentworth D; Abrams D I. National Institutes of Health, Bethesda, MD. 4th Conf Retro and Opportun Infect (1997). pp. 112 (Abstract No. 260). Pub. country: United States. Language: English.

AB The use of protease inhibitors (PIs) has rapidly increased in the management of HIV infection. We assessed their use among 1,103 CPCRA patients, who were not enrolled in a CPCRA antiretroviral (AR) trial and who attended a follow-up visit between April and August 1996. Median CD4 cell count was 168 cells/mm3; 14% were women; 31% were African-Americans and 9% were Latino; 19% reported a history of intravenous drug use (IDU); and 90% were prescribed AR treatment. Of the 990 patients prescribed AR treatment, 416 (42%) were prescribed a PI; use ranging from 50% of those with CD4 cell counts less than 100 cells/mm3 to 35% of those with CD4 cell counts 300-499 cells/mm3. Among the 416 patients prescribed a PI, 183 (44%) were prescribed **saquinavir**; 148 (36%) indinavir; and 93 (22%) **ritonavir**. Eight patients were prescribed greater than or equal to 2 PIs. Most patients prescribed a PI were also prescribed 2 nucleoside agents (76%). 65% of those receiving a single PI were prescribed AZT & 3TC, followed by 24% prescribed D4T & 3TC. Approximately 20% of patients prescribed a PI were taking it with one nucleoside agent, most commonly 3TC, followed by D4T. A multivariate analysis was carried out to determine whether use of PIs among those prescribed AR treatment varied by gender, race, risk group, and CD4 cell count. These analyses adjusted for CPCRA center and protocol. PIs were more likely to be prescribed for patients with lower CD4 cell counts (p=.0004) and less likely to be prescribed for African-Americans (p=.0001). In summary, we found that currently in the CPCRA, PIs are most commonly used in combination with two nucleoside agents and are prescribed less often to African-Americans and more often to those with advanced disease.

L84 ANSWER 21 OF 69 AIDSLINE

97:16211 Document No.: AIDS-97926411. Activity of ABT-378 against HIV protease containing mutations conferring resistance to **ritonavir**. Chen C; Niu P; Kati W; Norbeck D; Sham H; Kempf D; Kohlbrenner W; Plattner J; Leonard J; Molla A. Abbott Laboratories, Abbott Park, IL. 4th Conf Retro and Opportun Infect (1997). pp. 103 (Abstract No. 208). Pub. country: United States. Language: English.

AB **Ritonavir** is a potent inhibitor of HIV protease. Clinical studies of AIDS patients treated with **ritonavir** showed a dramatic reduction in circulating viral RNA level with a concomitant increase in CD4 cells. However, prolonged monotherapy with suboptimal doses of **ritonavir** led to the emergence of viral mutants with reduced susceptibility to the inhibitor. Sequence analyses indicated that the high level resistance was due to the combined effect of mutations at several positions of the protease gene with early changes at valine residue 82. Mutant proteases which contained V82A, V82F, V82S and V82T were expressed and purified from E. coli to assess the effects of these substitutions on the properties of the enzyme. Using a fluorogenic substrate, a 10-250

fold reduction in sensitivity to **ritonavir** was detected for these mutants relative to the wild type enzyme. The catalytic efficiency, k(cat)/K(m), for the mutants also decreased by a factor of 2 to 25. Inhibition constants were also measured for **saquinavir**, indinavir, VX-478 and nelfinavir. Both **saquinavir** and VX-478 remained potent inhibitors against all mutant enzymes. Although indinavir and nelfinavir displayed resistance profiles similar to **ritonavir** against this panel of mutant enzymes, the maximum loss of potency was only 23 fold as judged by increases in K(i) values. In related studies, ABT-378, a second generation C(2)-symmetry based protease inhibitor, was found to be a potent inhibitor of all mutant enzymes studied, with K(i) values below 30 pM. This suggests that ABT-378 might suppress the emergence of resistance against **ritonavir** when used in combination.

L84 ANSWER 22 OF 69 AIDSLINE

97:15959 Document No.: AIDS-97926159. Rapid improvement in cell mediated immune function with initiation of **ritonavir** plus **saquinavir** in HIV immune deficiency. Angel J B; Parato K; Kumar A; Filion L G; Diaz-Mitoma F; Pham B; Sun E; Leonard J; Cameron D W. Ottawa General Hospital, Ottawa, Ontario, Canada. 4th Conf Retro and Opportun Infect (1997). pp. 71 (Abstract No. 33). Pub. country: United States. Language: English.

AB Background: Loss of cell mediated immunity (CMI) leads to the development of HIV related opportunistic infections and the inability to restrict HIV replication. Methods: We investigated the effect of potent antiretroviral therapy (**ritonavir** plus **saquinavir**) on several functional measures of CMI in HIV-infected patients with 100-500 CD4+ T cells/microliter . Proliferative responses to PHA, p24 Ag and tetanus toxoid (TT), as well as IL-2, IL-12 and IL-10 production were measured at baseline, 4 and 24 weeks and correlated with changes in viral load and CD4+ T cell count. Results: Median decrease in plasma viral load was greater than 2 log(10) at 4 wks and greater than 4 log(10) at 12 wks. At 4 wks, proliferative responses to PHA, p24 Ag and TT developed or improved in 27/41, 14/41 and 3/8 patients respectively. Cytokine data is tabulated: (Table: see text) A dramatic (greater than 8-fold) increase in the response to PHA correlated with a greater CD4+ T cell rise (p=0.0075). Data collected at 24 wks is being similarly analyzed. Conclusion: These data illustrate an immunologic effect of potent anti-HIV therapy which appears rapidly with the onset of antiviral effect, suggesting that HIV-induced functional immune suppression is dynamic and potentially reversible.

L84 ANSWER 23 OF 69 AIDSLINE

97:15861 Document No.: AIDS-97926061. Metabolism in vitro and in vivo. Collins J M. Laboratory of Clinical Pharmacology, Food and Drug Administration, Rockville, MD. 4th Conf Retro and Opportun Infect (1997). pp. 221 (Abstract No. S42). Pub. country: United States. Language: English.

AB The technology for determination of metabolic pathways and drug-drug interactions in vitro has matured during the time frame for development of HIV protease inhibitors. Drug developers have always been interested in metabolism, with particular emphasis upon avoiding unpleasant surprises due to drug interactions. Until recently, metabolic studies in vivo have been the only reliable tool for obtaining an assessment of the risks. For example, glucuronidation of zidovudine was not discovered until Phase I

testing. For some the most common pathways, the definitive metabolic determination in vitro can permit and extrapolation to a series of likely results in vivo, both in terms of inhibition and induction. Any reduction in the number of clinical studies is welcome, as well as the prior knowledge of situation to avoid. Studies in our lab (Fitzsimmons and Collins, in press) and elsewhere have demonstrated that **saquinavir** is metabolized by cytochrome P450 3A4. Compilation of these lab findings as well as metabolic/interaction data obtained in vivo has produced as drug label which is highly informative for prescribers and patients, but very challenging for practical use. In addition to providing safety information, the metabolic data also provide a basis for innovative therapeutic maneuvers, such as the combination of **ritonavir** with **saquinavir**. The situation for **saquinavir** and other HIV protease inhibitors mirrors trends occurring across all therapeutic classes.

L84 ANSWER 24 OF 69 AIDSLINE
97:15736 Document No.: MED-97300526. Adverse effects and drug interactions of medications commonly used in the treatment of adult HIV positive patients: Part 2. Heylen R; Miller R. Pharmacy Department, University College London Hospitals (NHS) Trust, Middlesex Hospital Site, UK. GENITOURINARY MEDICINE (1997). Vol. 73, No. 1, pp. 5-11. Journal code: GEM. ISSN: 0266-4348. Pub. country: ENGLAND: United Kingdom. Language: English.

L84 ANSWER 25 OF 69 AIDSLINE
97:15379 Document No.: MED-97253476. Antiretroviral therapy: a guide to the most important trials. Rutschmann O; Hirschel B. Division of Infectious Diseases, Hopital Cantonal Universitaire de Gen`eve. SCHWEIZERISCHE MEDIZINISCHE WOCHENSCHRIFT. JOURNAL SUISSE DE MEDECINE (1997). Vol. 127, No. 11, pp. 436-43. Journal code: UEI. ISSN: 0036-7672. Pub. country: Switzerland. Language: English.
AB AIDS and HIV infection have stimulated an unprecedented amount of research. In this review we have selected a few publications illustrating key issues. Viral load monitoring is useful because short-term changes in viremia, caused by antiretroviral treatment, predict long-term outcome. Combination therapy with AZT plus either ddI or ddC produces better results than therapy with AZT only, but the differences are slight and appeared only after several years of follow-up. In contrast, the effect of adding 3TC to AZT-containing regimens was statistically significant after only one year, halving mortality and the incidence of new AIDS-defining opportunistic infection. Adding **ritonavir** had a similar effect after 20 week's follow-up in far-advanced HIV infection. The most potent regimens combine AZT, 3TC, and either **ritonavir** or indinavir; in the majority of patients thus treated viremia became undetectable (< 500 copies/ml).

L84 ANSWER 26 OF 69 AIDSLINE
97:14549 Document No.: AIDS-97702378. Protease inhibitors: resistance, resistance, resistance. Gilden D; Falkenberg J; Torres G. GMHC Treat Issues (1997). Vol. 11, No. 2, pp. 5-10. Pub. country: United States. Language: English.
AB Current anti-HIV drugs are plagued by problems with development of resistance. Reports at the 4th Annual Conference on Retroviruses and Opportunistic Infections proposed various ways to use protease inhibitor-containing combinations to build a high enough genetic barrier against HIV breakthrough. Two studies confirmed that potent

highly active antiretroviral therapy combination therapies can be beneficial even to people with advanced AIDS and with extensive past exposure to anti-HIV therapy. While nelfinavir has shown itself to be a respectable protease inhibitor, optimum dosage questions still persist and the issue of cross-resistance is a concern. Abbott laboratories revealed its new protease inhibitor ABT-378. ABT-378 is highly active against HIV, even more so than **ritonavir**. Toxicity information about ABT-378 or what drug levels to use to avoid resistance are not known. Two studies that achieved some success in HIV treatment by combining protease inhibitors are also reported. Currently, there are 12 possible double protease inhibitor combinations using the three protease inhibitors on the market and nelfinavir. However, while **ritonavir** works with **saquinavir** and possibly ABT-378, there may be interference between protease inhibitors because they compete for the same binding sites on HIV protease, thus weakening the overall effect to less than the sum of their individual effects.

L84 ANSWER 27 OF 69 AIDSLINE
97:14532 Document No.: AIDS-97702361. Combined protease results continue to hold up. McGuire S. Posit Aware (1997). Vol. 8, No. 1, pp. 15. Pub. country: United States. Language: English.
AB A study of the combination **ritonavir** and **saquinavir** is showing dramatic viral load reductions and CD4 increases. This is the first controlled clinical trial combining protease inhibitors. Several dosage combinations were studied, and some viral load analyses showed reductions of 99.9 percent. Firm judgment about efficacy and durability can only be reliably made after 12 months of data and analysis are available.

L84 ANSWER 28 OF 69 AIDSLINE
97:14441 Document No.: AIDS-97229518. Combination study of Invirase and **Norvir** starting [news]. Anonymous. CKD (1996). Vol. 10, No. 3, pp. 187. Journal code: CKD. ISSN: 1087-2914. Pub. country: United States. Language: English.

L84 ANSWER 29 OF 69 AIDSLINE
97:13909 Document No.: AIDS-97220430. Combination of two protease inhibitors reduces HIV viral load by 99.9% [news]. Anonymous. CKD (1996). Vol. 10, No. 6, pp. 375. Journal code: CKD. ISSN: 1087-2914. Pub. country: United States. Language: English.

L84 ANSWER 30 OF 69 AIDSLINE
97:13877 Document No.: AIDS-97229571. **Saquinavir** plus **ritonavir** open-label study recruiting [news]. Anonymous. CKD (1996). Vol. 10, No. 5, pp. 308. Journal code: CKD. ISSN: 1087-2914. Pub. country: United States. Language: English.

L84 ANSWER 31 OF 69 AIDSLINE
97:13337 Document No.: MED-97125597. What we know so far. Gazzard B. Chelsea and Westminster Hospital, London, UK. AIDS (1996). Vol. 10, Suppl. 1, pp. S3-7. Journal code: AID. ISSN: 0269-9370. Pub. country: United States. Language: English.
AB AIM: To review current knowledge of anti-HIV therapy and the implications for patient management. WHAT IS KNOWN: In three large clinical studies, combination therapy with zidovudine plus didanosine or zalcitabine improved survival and delayed clinical events in comparison with zidovudine alone, with greater benefits in zidovudine-naive than zidovudine-experienced patients. Initial

studies suggest addition of an HIV protease inhibitor to combination therapy with two nucleoside analogues may result in greater reduction in viral loads, raising hopes about eradication therapy. Two clinical endpoint studies involving protease inhibitors are available. In one of these, **saquinavir**/zalcitabine combination therapy offered significant clinical benefits over monotherapy with either drug and in the other **ritonavir** improved survival in individuals with late HIV infection. IMPLICATIONS AND REMAINING QUESTIONS: It remains unclear at what stage therapy should be started. Evidence from clinical studies suggests initial therapy should be a combination regimen, probably two nucleoside inhibitors. Data from surrogate marker studies suggest that even greater reductions in viral load and increments in CD4+ count can be seen using triple therapy, either with two nucleosides and a non-nucleoside reverse transcriptase inhibitor, or two nucleoside analogues and a protease inhibitor. It remains unclear whether there is a qualitative difference between reducing viral load below detectable levels and more modest reductions in viral load, and whether immune destruction caused by HIV can be reversed and if sustained suppression of HIV replication can be achieved. CONCLUSIONS: It is now possible to offer real hope of improvements in survival to HIV-infected patients, through the use of combinations of antiretroviral agents, but more evidence from ongoing and further studies is still needed.

L84 ANSWER 32 OF 69 AIDSLINE

97:13335 Document No.: MED-97125600. Risks and synergies from drug interactions. Sahai J. Clinical Investigation Unit, Ottawa General Hospital, Ontario, Canada. AIDS (1996). Vol. 10, Suppl. 1, pp. S21-5. Journal code: AID. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB AIM: To review what is known from in vitro and in vivo studies about the interactions, both potentially beneficial and potentially harmful, of antiretroviral agents with each other and with other classes of drugs. INTERACTIONS WITH NUCLEOSIDE ANALOGUES: Some interactions between nucleoside HIV reverse transcriptase inhibitors and between nucleoside analogues and HIV protease inhibitors result in greater antiretroviral activity (e.g. zalcitabine with **saquinavir**). Others may increase the risks of toxicity and there are a number of combinations of nucleoside agents with other drugs that should be used with caution or avoided completely. INTERACTIONS WITH PROTEASE INHIBITORS: These drugs are metabolized by cytochrome P450 CYP3A4 in the liver; because they have the potential to inhibit this enzyme they may interact with many other drugs that are metabolized by this pathway. **Ritonavir** also inhibits other cytochrome P450 enzymes and so interacts with numerous drugs from a range of classes. Potentially beneficial interactions between protease inhibitors include the increase in **saquinavir** levels brought about by **ritonavir**. CONCLUSIONS: Knowledge of additive and synergistic interactions between antiretroviral agents should facilitate development of therapeutic regimens with prolonged antiretroviral activity. Thorough investigation of possibly harmful interactions with co-administered drugs and education of clinicians and patients about the risks of these interactions is required.

L84 ANSWER 33 OF 69 AIDSLINE

97:13334 Document No.: MED-97125599. Rational approaches to resistance: using **saquinavir**. Boucher C. Department of Virology,

Eykman-Winkler Institute, University Hospital Utrecht, The Netherlands. AIDS (1996). Vol. 10, Suppl. 1, pp. S15-9. Journal code: AID. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB AIM: To review drug-resistance patterns of HIV protease inhibitors, with particular reference to **saquinavir**, and how resistance and cross-resistance patterns may influence disease management. RESISTANCE TO **SAQUINAVIR**: Resistance to **saquinavir** in vitro and in vivo is associated with mutations L90M and G48V in HIV protease. L90M is the predominant mutation in vivo. Clinically, G48V is uncommon and the double mutation rare. This pattern of mutation differs from those seen with other protease inhibitors. CROSS-RESISTANCE: Long-term treatment with **saquinavir** in most cases does not induce a significant decrease in sensitivity to **saquinavir** itself or other protease inhibitors. Where significant resistance to **saquinavir** does develop (i.e. fourfold increase in the median inhibitory concentration), there are observed instances of cross-resistance. Preliminary phenotypic studies of patients on combination therapy with **saquinavir** (plus zalcitabine and/or zidovudine) for 1 year indicate that > 80% should subsequently respond to indinavir, **ritonavir** or VX-478. CONCLUSIONS: Resistance to **saquinavir** develops slowly and in a minority of patients on long-term therapy. Reduced susceptibility to **saquinavir** is associated with mutations different from those associated with other HIV protease inhibitors. **Saquinavir** appears to be a good first-choice protease inhibitor for combination therapy with HIV reverse transcriptase inhibitors as it should provide prolonged antiretroviral activity without limiting subsequent therapeutic options.

L84 ANSWER 34 OF 69 AIDSLINE

97:13090 Document No.: MED-97062998. Protease inhibitors: a new weapon and a new strategy against HIV. Phillips K D. University of South Carolina, Columbia, USA. JOURNAL OF THE ASSOCIATION OF NURSES IN AIDS CARE (1996). Vol. 7, No. 5, pp. 57-71. Journal code: A7P. ISSN: 1055-3290. Pub. country: United States. Language: English.

AB Until recently, reverse transcriptase inhibitors have been the mainstay for treating HIV infection. Now, three protease inhibitors have been approved. Early evidence suggests that triple therapy delays the progression of HIV infection. An understanding of these new drugs and treatment strategies is imperative for clinicians. This article (1) reviews HIV's structure and replication process, (2) discusses currently approved reverse transcriptase and protease inhibitors, (3) describes the antiretroviral drugs' modes of action, (4) discusses important nursing implications for monitoring clients on these drugs, and (5) presents current scientific evidence regarding the effectiveness of combination therapy strategies.

L84 ANSWER 35 OF 69 AIDSLINE

97:13060 Document No.: MED-97125634. Advances in antiretroviral therapy and viral load monitoring. Hammer S M. Division of Infectious Diseases, Deaconess Hospital, Boston, MA, USA. AIDS (1996). Vol. 10, Suppl. 3, pp. S1-11. Journal code: AID. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB OBJECTIVE: To highlight recent developments in the field of antiretroviral therapy and viral load monitoring. METHODS: Review of studies detailing the efficacy of the antiretroviral agents and combinations furthest along in clinical development and the

application of plasma HIV RNA quantification as a disease marker. RESULTS: Developments in the field of antiretroviral therapy have led to substantial advances in the approach to management of HIV-infected persons. These include the end of the zidovudine (ZDV) monotherapy era; the demonstration of a survival benefit conferred by antiretroviral therapy in patients with CD4 counts of 200-500x10(6)/l; the further development of newer nucleoside analog combinations (e.g., ZDV-lamivudine, stavudine-didanosine, stavudine-lamivudine, ZDV-1592U89) and the non-nucleoside reverse transcriptase inhibitor class of compounds; and, perhaps most importantly, the advent of the protease inhibitor era. Trials of **ritonavir** and **saquinavir** have proven that clinical benefit can be conferred by protease inhibitors, and three-drug combination regimens, such as indinavir-ZDV-lamivudine, have shown the potential for degrees of viral suppression not previously seen. Newer protease inhibitors, such as nelfinavir and VX-478/GW141W94, hold promise for further advances. The concurrent development of assays to quantitatively measure plasma HIV RNA has provided laboratory tools to improve our understanding of disease pathogenesis, to assess the in vivo potency of treatment regimens and to characterize the risk of disease progression. CONCLUSIONS: Recent progress in HIV disease pathogenesis, antiretroviral therapy and viral load monitoring indicates the interdependence of these factors. The current optimism in the field is warranted but complex challenges must be met if the fulfilment of this hope is to be realized by the world community.

L84 ANSWER 36 OF 69 AIDSLINE

97:10723 Document No.: MED-97046545. **Ritonavir**. Lea A P; Faulds D. Adis International Limited, Auckland, New Zealand. DRUGS (1996). Vol. 52, No. 4, pp. 541-6, discussion pp. 547-8. Journal code: EC2. ISSN: 0012-6667. Pub. country: New Zealand. Language: English.

AB **Ritonavir** is a protease inhibitor with an HIV-1 resistance profile similar to that of indinavir, but different from that of **saquinavir**. **Ritonavir** has good oral bioavailability, and may increase the bioavailability of other protease inhibitors including **saquinavir**, nelfinavir, indinavir and VX-478. Clinically significant drug interactions have been predicted between **ritonavir** and a range of medications. In patients with HIV-1 infection, **ritonavir** markedly reduced viral load within 2 weeks of treatment onset and also increased CD4+ cell counts. In a large placebo-controlled trial in patients with advanced HIV infection, the addition of **ritonavir** to existing therapy reduced the risk of mortality by 43% and clinical progression by 56% after 6.1 months. Triple therapy with **ritonavir** plus zidovudine, in combination with lamivudine or zalcitabine, reduced HIV viraemia to below detectable levels in most patients with acute, and some patients with advanced HIV infection in 2 small trials. Early results suggest combination therapy with **ritonavir** and **saquinavir** increases CD4+ cell counts and decreases HIV RNA levels in patients with previously untreated HIV infection.

L84 ANSWER 37 OF 69 AIDSLINE

97:10456 Document No.: AIDS-97701975. **Ritonavir** and **saquinavir** combination: 12-week data at ICAAC. James J S. AIDS Treat News (1996). No 256, pp. 3. ISSN: 1052-4207. Pub. country: United States. Language: English.

AB Data from a multi-center study of combination therapy of two protease inhibitors is encouraging. The viral load reductions have been greater than would have been expected from either **ritonavir** or **saquinavir** alone. The two drugs are being studied in combination because **ritonavir** increases blood levels of **saquinavir** and because these protease inhibitors have somewhat different patterns of viral resistance development. Each drug alone has shown benefit in clinical trials. It is possible that this combination might work even better if combined with one or two nucleoside analogs.

L84 ANSWER 38 OF 69 AIDSLINE
97:10432 Document No.: AIDS-97701951. Nevirapine-plus-protease studies under way. Anonymous. AIDS Alert (1996). Vol. 11, No. 10, pp. 119. ISSN: 0887-0292. Pub. country: United States. Language: English.
AB Manufacturers of nevirapine (Viramune) report that studies of the interaction of this non-nucleoside reverse transcriptase drug and indinavir and **saquinavir** are underway. About 21 patients have been treated with nevirapine and **saquinavir**, and 22 patients have been treated with nevirapine and **ritonavir**. These studies will determine whether nevirapine can be safely taken with protease inhibitors. Preliminary interaction studies suggested that nevirapine decreases the drug levels of **saquinavir** by about 17 percent. Currently, nevirapine is labeled for combination with nucleoside analogues only.

L84 ANSWER 39 OF 69 AIDSLINE
97:10291 Document No.: AIDS-97702185. Anti-HIV agents at ICAAC. Smart T. GMHC Treat Issues (1996). Vol. 10, No. 10, pp. 7-10. Pub. country: United States. Language: English.
AB Many treatments highlighted at the ICAAC conference were designed to suppress the replication of HIV completely, but growing numbers of people are reporting rebound increases after initial decreases in viral load. However, new drugs are being developed which may be more effective, better tolerated, and less likely to lead to resistance. Agouron Pharmaceuticals has opened an expanded access program for its new protease inhibitor, Viracept; the program is open to people who cannot tolerate the other approved drugs. Gilead Sciences is warning physicians and patients that cidofovir should not be used with other kidney-toxic drugs.

L84 ANSWER 40 OF 69 AIDSLINE
97:10285 Document No.: AIDS-97702167. A patient's guide to protease inhibitors. Elperin A; Sax P. Brigham and Women's Hospital, Boston, MA. AIDS Clin Care (1996). Vol. 8, No. 10, pp. 83-4. ISSN: 1043-1543. Pub. country: United States. Language: English.
AB Dosage guidelines and side effects of three currently available protease inhibitors (**saquinavir**, **ritonavir**, indinavir) reveal very different patterns. Dosage regimens are as follows: **saquinavir**, 3 capsules every 8 hours with food; **ritonavir**, 6 capsules every 12 hours with food; and indinavir, 2 capsules every 8 hours on an empty stomach. **Ritonavir** has the severest side effects, including nausea, diarrhea, and initially, tingling feeling of the mouth, arms, or legs. The drugs work best when taken with well-studied medicines such as AZT, d4T, and ddI.

L84 ANSWER 41 OF 69 AIDSLINE
97:10153 Document No.: AIDS-97702127. Antiviral update. Anonymous. PI

Perspect (1996). No 20, pp. 8-9. Pub. country: United States. Language: English.

AB As combination therapy for treating HIV/AIDS grows, data on how these drugs interact becomes necessary and more complex. Information is provided on drug interactions using nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors, NNRTIs and nucleoside reverse transcriptase inhibitors, DMP 266 and indinavir, AZT and delavirdine, and **ritonavir** and **saquinavir**. New concerns for some combinations have arisen concerning AZT with d4T and nevirapine with indinavir. Trial results and questions about using these drugs are provided.

L84 ANSWER 42 OF 69 AIDSLINE

97:10147 Document No.: AIDS-97702136. **Saquinavir** plus **ritonavir** reduce viral load by 99.9 percent. Vazquez E. Posit Aware (1996). Vol. 7, No. 6, pp. 8-9. Pub. country: United States. Language: English.

AB A combination of two protease inhibitors, **saquinavir** (Invirase) and **ritonavir** (**Norvir**), may produce a median drop in viral load of 99.9 percent. Several dosage variations were tested. The most common side effects of the combination regimen included tingling around the mouth, diarrhea, fatigue, and nausea. A low level of toxicity was found. This combination may be used for people who have failed other protease inhibitor therapy or have developed a resistance to nucleoside analogues.

L84 ANSWER 43 OF 69 AIDSLINE

97:9560 Document No.: MED-97144574. HIV-1 protease inhibitors. A review for clinicians. Deeks S G; Smith M; Holodniy M; Kahn J O. University of California, San Francisco, USA. JAMA (1997). Vol. 277, No. 2, pp. 145-53. Journal code: KFR. ISSN: 0098-7484. Pub. country: United States. Language: English.

AB OBJECTIVE: The clinical care of people infected with human immunodeficiency virus (HIV) has been substantially affected by the introduction of HIV-specific protease inhibitors (PIs). The 4 PIs available are **saquinavir** mesylate, **ritonavir**, indinavir sulfate, and nelfinavir mesylate. Comparison studies have not been reported; therefore, an assessment of the available data to aid clinicians and patients in choosing appropriate treatment will be presented. DATA SOURCES: A systematic review of peer-reviewed publications, abstracts from national and international conferences, and product registration information through September 1996. STUDY SELECTION AND DATA EXTRACTION: Criteria used to select studies include their relevance to PIs, having been published in the English language, and pertinence for clinicians. Data quality and validity included the venue of the publication and relevance to clinical care. DATA SYNTHESIS: Oral adminstration of **ritonavir**, indinavir, or nelfinavir generates sustainable drug serum levels to effectively inhibit the protease enzyme; however, **saquinavir** may not generate sustained levels necessary to inhibit the protease enzyme. Patients treated with **ritonavir**, indinavir, or nelfinavir experience similar reductions in viral load and increases in CD4+ lymphocytes; smaller effects occur among those treated with **saquinavir**. Two randomized placebo-controlled studies conducted among patients with severe immune system suppression and substantial zidovudine treatment experience demonstrated reduced HIV disease progression and reduced mortality with PI treatment. Genotypic resistance to PIs occurs; the clinical relevance of resistance is unclear. The costs of these agents including required

monitoring impose new and substantial costs. CONCLUSIONS: The PIs have emerged as critical drugs for people with HIV infection. Optimal use involves combination with reverse transcriptase inhibitors. Resistance develops to each agent, and cross-resistance is likely. These agents must be used at full doses with attention to ensuring patient compliance. The expense of these agents may be offset by forestalling disease progression and death and returning people to productive life. Selecting the initial PI must be individualized, and factors to consider include proven activity, possible toxicities, dosing regimens, drug interactions, and costs.

L84 ANSWER 44 OF 69 AIDSLINE

97:9436 Document No.: MED-97128746. [HIV: to administer protease inhibitors early (news)]. HIV: Protease-Inhibitoren fruh einsetzen. Anonymous. DEUTSCHE MEDIZINISCHE WOCHENSCHRIFT (1996). Vol. 121, No. 49, pp. A49. Journal code: ECL. ISSN: 0012-0472. Pub. country: GERMANY: Germany, Federal Republic of. Language: German.

L84 ANSWER 45 OF 69 AIDSLINE

97:9347 Document No.: MED-97106655. AIDS therapy with two, three or four agent combinations, applied in short sequences, differing from each other by drug rotation. I. First of two parts: a phase I trial equivalent, concerning five virostatics: AZT, ddI, ddC, acriflavine and an ellipticine analogue. Mathe G; Pontiggia P; Orbach-Arbouys S; Triana K; Ambetima N; Morette C; Hallard M; Blanquet D. Institut de Cancerologie et d'Immunologie & Hopital Suisse de Paris, Issy-les-Moulineaux, France. BIOMEDICINE AND PHARMACOTHERAPY (1996). Vol. 50, No. 5, pp. 220-7. Journal code: A59. ISSN: 0753-3322. Pub. country: France. Language: English.

AB We have individually treated ten AIDS patients whose CD4 numbers were inferior to 200/mm3, with the five following HIV1 virostatics: a) azido-deoxythymidine (AZT), dideoxyinosine (ddI) and dideoxycytidine (ddC), which affect the same viral target, retrotranscriptase, b) acriflavine (ACF) and methyl-hydroxy-ellipticine (MHE) which we have discovered to be strong virostatics in vivo, in mice, against Friend's virus, and in man, against AZT resistant HIV1. We have shown that their combinations with AZT, hitting three viral targets, reduces in mice, the blood Friend's virus load below detectable level. Due to the short doubling time of HIV1, AIDS therapy must be continuous, and to allow the best tolerance, the five virostatic combinations were applied in short, three-week sequences, each differing as much as possible from the former and from the following one, due to drug rotation [1]. Among the ten patients, a) three received the two-drug combinations for 15 to 30 months, followed by the three-drug combinations, b) three received the three-drug combinations from the beginning, c) four received the four-drug combinations also from the beginning, two having less than 10 CD4/mm3 at initiation of treatment, and two having more than 100. The tolerance was remarkable: the only side-effect being macrocytosis. The application of the two-drug combination sequences maintained stable CD4 levels in two subjects whose viral load (the evaluation of which had became available) was, at the end of this period, of 4,486 and 39,238 RNA copies. The third subject who had received, an intensive UV irradiation for a psoriasis, presented an irreversible decrease in his CD4 count and a high viral load (1,352,495 RNA copies/mL) at the end of the two-drug period. Fifteen to 25 months after the shift to the three-drug combinations, the viral load decreased, from 39,328 to 13,291 in one of the non-UV irradiated subjects, and from 1,352,495 to 314,387 in

the irradiated one. No subject had an increase in CD4 number. In the three patients having initially received the three-drug combinations, a very strong decrease of viral load was registered after periods of observation varying from 77 to 40 months, while the CD4 counts increased moderately in two subjects, and noticeably in the third (from 126 to 266). Out of the four subjects initially treated with four-drug combinations, the two with less than 10 CD4/mm3 had a moderate decrease in viral load in about three months, and the CD4 increased from 9 to 34/mm3 in one. But the two subjects, because of opportunistic infections and psychological reasons, abandoned their treatments. In the two subjects who had more than 100 CD4/mm2 at initiation of the four-drug combination treatment, the viral load decreased to undetectable levels after four months: but their CD4 counts, after some oscillations, had very moderately increased at the end of the observation period (respectively, from 200 to 222, and from 129 to 134). In practice, these results suggest the interest of conducting phase II or III studies of AIDS treatment protocols, starting with the four-drug combination model, and attempting to maintain the effect with the three-drug combination one. As for theoretical considerations, one must underline the contrast between the remarkable reduction of the viral load and the usually moderate increase of the CD4 counts. The study but not the trial has been interrupted, due to the unavailability of three antiproteases, **saquinavir**, **ritonavir** and indinavir, which are now introduced in the same type of combinations, one by one, in replacement of one of the studied agents as shown in figure 1. The effect of increasing the total number of virostatics from five to eight will be published in the second part of this article series.

L84 ANSWER 46 OF 69 AIDSLINE

97:7151 Document No.: MED-97080414. [HIV protease inhibitors. A new drug class in antiretroviral therapy]. HIV-Proteaseinhibitoren. Eine neue Substanzklasse in der antiretroviralen Therapie. Mauss S; Seidlitz B; Jablonowski H; Haussinger D. Klinik fur Gastroenterologie, Hepatologie und Infektiologie, Universitat Dusseldorf. DEUTSCHE MEDIZINISCHE WOCHENSCHRIFT (1996). Vol. 121, No. 44, pp. 1369-74. Journal code: ECL. ISSN: 0012-0472. Pub. country: GERMANY: Germany, Federal Republic of. Language: German.

L84 ANSWER 47 OF 69 AIDSLINE

97:5066 Document No.: ICA11-96920812. Advances in antiretroviral therapy and viral load monitoring. Hammer S. Division of Infectious Diseases, Deaconess Hospital and Harvard Medical School, Boston, MA, USA. Fax: 617-632-0766. E-mail:. shammer@nedmaol.nedh.harvard.edu.. Int Conf AIDS (1996). Vol. 11, No. 1, pp. 2 (Abstract No. Mo.01). Pub. country: Canada. Language: English.

AB Recent developments in the field of antiretroviral therapy have led to substantial advances in the approach to management of persons. These include: the end of the ZDV monotherapy era; the demonstration of a survival benefit conferred by antiretroviral therapy in patients with 200-500 CD4 cells/mm3, the further development of newer nucleoside analog combinations (e.g. ZDV/3TC, d4T/ddI, d4T/3TC) and the non-nucleoside reverse transcripatse inhibitor class of agents; and, perhaps most importantly, the advent of the protease inhibitor era. Trials of **ritonavir** and **saquinavir** have proven that clinical benefit can be conferred by protease inhibitors and three drug combination regimens, such as indinavir/ZDV/3TC, have shown the potential for

degrees of viral suppression not heretofore seen. Newer protease inhibitors, such as nelfinavir and VX-478, hold promise for further advances. The concurrent development of assays to quantitatively measure plasma HIV RNA has provided laboratory tools to improve our understanding of disease pathogenesis, assess the in vivo potency of treatment regimens and characterize the risk of disease progression. A new sense of hope has been raised by these advances but complex challenges must be met if the fulfilment of this hope is to be realized by the world community.

L84 ANSWER 48 OF 69 AIDSLINE
96:12610 Document No.: AIDS-96701938. Delavirdine/protease inhibitor interactions. Gilden D. GMHC Treat Issues (1996). Vol. 10, No. 9, pp. 11-2. Pub. country: United States. Language: English.
AB On September 27, 1996, the Food and Drug Administration's (FDA) Antiviral Drugs Advisory Committee meets to consider licensing the non-nucleoside reverse transcriptase inhibitor (NNRTI), delavirdine (Rescriptor). How both delavirdine and nevirapine, another NNRTI, affect the body's metabolism of protease inhibitors is an issue that remains unresolved. Pharmacia & Upjohn released preliminary results of combining delavirdine with the three marketed protease inhibitors: **saquinavir**, **ritonavir**, and indinavir. Tests show delavirdine raised **saquinavir** levels sixfold, had no effect on **ritonavir**, and doubled the effective dose of indinavir.

L84 ANSWER 49 OF 69 AIDSLINE
96:12585 Document No.: AIDS-96701913. **Ritonavir** plus **saquinavir**: two trials with different results. Mascolini M. AIDS Treat News (1996). No 254, pp. 5-6. ISSN: 1052-4207. Pub. country: United States. Language: English.
AB Two trials testing the combination of the protease inhibitors, **ritonavir** and **saquinavir**, recently came to different conclusions, possibly explained by differences in trial size, drug dosage, and disease stage of the participants. Studies have suggested that **ritonavir** greatly increases blood levels of **saquinavir**, making a combination of the two especially attractive. One trial of 63 individuals, led by Dr. William Cameron of the University of Ottawa, found that two different doses of the drugs decreased viral load up to 99 percent and increased CD4 counts by 80 to 100 points. However, a smaller, nine-person study led by Dr. Bernard Hirschel of the University Hospital of Geneva, showed that viral load was reduced by at least 90 percent, though it quickly rebounded in some patients. The trials suggest that resistance to the drugs does not develop immediately, although it could emerge later. Researchers are now attempting to find the proper dosing strategy--one that is strong enough to suppress viral replication and prevent resistance while being mild enough to be tolerated.

L84 ANSWER 50 OF 69 AIDSLINE
96:12578 Document No.: AIDS-96701906. Protease inhibitors. Anonymous. Treat Rev (1996). No 22, pp. 2-7. Pub. country: United States. Language: English.
AB There are now nine approved anti-HIV drugs, all of which are meant to keep the level of HIV as low as possible, prevent further damage to the immune system, and stop the progression of the disease. The combination of drugs prescribed depends on which the doctor feels will best stop disease progression based on the side effects, the

patient's treatment history, and the patient's current symptoms. Drug resistance is always a threat, and guidelines are given to assess the risks of a patient developing resistance. Each of the approved drugs is highlighted, along with guidelines for their use, their strengths and weaknesses, and special assistance programs offered by the pharmaceutical manufacturer.

L84 ANSWER 51 OF 69 AIDSLINE
96:12363 Document No.: MED-96425523. [For the first time a combination of 2 protease inhibitors investigated (news)]. Erstmals Kombination von zwei Protease-Hemmern untersucht. Schenk M. DEUTSCHE MEDIZINISCHE WOCHENSCHRIFT (1996). Vol. 121, No. 34-35, pp. A36. Journal code: ECL. ISSN: 0012-0472. Pub. country: GERMANY: Germany, Federal Republic of. Language: German.

L84 ANSWER 52 OF 69 AIDSLINE
96:11826 Document No.: MED-96283736. In vitro antiviral activity of 141W94 (VX-478) in combination with other antiretroviral agents. St. Clair M H; Millard J; Rooney J; Tisdale M; Parry N; Sadler B M; Blum M R; Painter G. Division of Virology, Glaxo Wellcome Inc., NC 27709, USA. ANTIVIRAL RESEARCH (1996). Vol. 29, No. 1, pp. 53-6. Journal code: 6I7. ISSN: 0166-3542. Pub. country: Netherlands. Language: English.
AB 141W94 (VX-478) is a novel HIV-1 protease inhibitor with an IC50 of 0.08 microM against HIV-1 (strain IIIB) and a mean IC50 of 0.012 microM against six HIV clinical isolates. 141W94 was synergistic on the basis of isobologram analysis with each of the following reverse transcriptase inhibitors: AZT, 935U83, 524W91, 1592U89 and ddI, 141W94 was also synergistic with **saquinavir** and additive with either indinavir or **ritonavir**. Resistance to 141W94 has been reported in vitro passage experiments. The binding of 141W94 to human alpha 1-acid glycoprotein was relatively weak (Kd = 4 microM) and the off-rate for the drug is very fast (> or = 100 s-1). Only a 2-fold reduction of in vitro antiviral activity was observed in the presence of 45% human plasma. No serious drug associated adverse experiences were reported in a Phase I placebo-controlled, single-dose escalation, pharmacokinetic and safety study. The average concentration of 141W94 at 8 and 12 h after single doses of 900 and 1200 mg, respectively, was in excess of 10 times the IC50. As 141W94 is synergistic with a variety of anti-HIV-1 agents and exhibits a unique cross resistance profile compared to other protease inhibitors, 141W94 is considered a good candidate for combination therapy.

L84 ANSWER 53 OF 69 AIDSLINE
96:11534 Document No.: AIDS-96701811. Nipping HIV in the bud. Smart T. GMHC Treat Issues (1996). Vol. 10, No. 8, pp. 3-6. Pub. country: United States. Language: English.
AB HIV may be ultimately cleared in recently infected people with the use of antiviral treatments, according to a general practitioner from San Francisco. Newly infected patients have a homogenous virus population that should be susceptible to all the drugs being used. The initial test regimen, used on eight participants who now have undetectable viral loads, was AZT/3TC/**ritonavir**. Other researchers tested less potent combinations; many showed impressive results. A chart shows data from the protease inhibitor combination trials.

L84 ANSWER 54 OF 69 AIDSLINE

96:9652 Document No.: AIDS-96701795. Matching up **ritonavir** with **saquinavir**. Anonymous. GMHC Treat Issues (1996). Vol. 10, No. 4, pp. 8. Pub. country: United States. Language: English.

AB A clinical trial is screening applicants for a study combining the protease inhibitors **ritonavir** and **saquinavir**. **Ritonavir** will raise the levels of **saquinavir** in the blood by about ten times and make the drug more effective. **Saquinavir**'s increased effectiveness may make it possible to decrease the **ritonavir** dosage. All subjects will receive both drugs in an escalating regimen. The trial will be conducted at multiple sites in the U.S. and in Ottawa. Further information can be obtained by calling Abbott Laboratories' consumer hotline.

L84 ANSWER 55 OF 69 AIDSLINE

96:9624 Document No.: AIDS-96701707. Protease inhibitors: **ritonavir** and **saquinavir** combination trial recruiting--seven U.S., Canada sites incl. San Francisco. Anonymous. AIDS Treat News (1996). no 245, pp. 1-3. ISSN: 1052-4207. Pub. country: United States. Language: English.

AB Abbott Laboratories, Inc. is recruiting HIV-positive volunteers to participate in the first trial using a combination of the HIV protease inhibitors **ritonavir** and **saquinavir**. Patients will be enrolled in seven sites in the U.S. and Canada. More information can be obtained by calling the International Association of Physicians in AIDS Care or the HIV Institute at Davies Medical Center.

L84 ANSWER 56 OF 69 AIDSLINE

96:9591 Document No.: AIDS-96701673. FDA approves 2 new protease inhibitors: **ritonavir** (**Norvir**) and Crixivan (Indinavir sulfate). Food and Drug Administration. Schouten J T. STEP Perspect (1996). Vol. 8, No. 1, pp. 7-8. Pub. country: United States. Language: English.

AB The Food and Drug Administration (FDA) approved two new protease inhibitors for treatment of AIDS. **Ritonavir** (**Norvir**) and indinavir (Crixivan) have been approved for both monotherapy and combination therapy, and appear to have relatively few side effects. Reports on clinical trials of both drugs are reported. **Saquinavir** (Invirase) also has FDA approval, but currently has a low absorption rate; better formulations are expected to increase absorption. Early trials indicate that triple drug combinations may suppress HIV replication to very low levels.

L84 ANSWER 57 OF 69 AIDSLINE

96:9541 Document No.: AIDS-96701623. Two protease inhibitors given high expectations. Anonymous. AIDS Alert (1996). Vol. 11, No. 6, pp. 63. ISSN: 0887-0292. Pub. country: United States. Language: English.

AB **Saquinavir**'s manufacturer, Hoffmann-La Roche of Nutley, NJ, has begun a new trial that will study the effectiveness of **saquinavir** (Invirase) and **ritonavir** (**Norvir**) in combination. The study, which began recruitment in seven cities, will enroll 120 patients, both drug-experienced and naive, with CD4 counts between 100 and 500. According to researchers at the Aaron Diamond AIDS Research Center, in vitro studies show that they cannot grow virus in the presence of the two drugs. Of great concern is the safety issue. Researchers will closely watch toxicity levels and other possible adverse reactions. They warn patients not to experiment with the two drugs until the trial's results are known. The seven cities participating in the trial are:

Pittsburgh; New York; Boston; Fairfax, VA; Los Angeles; San Francisco; and Ottawa, Canada.

L84 ANSWER 58 OF 69 AIDSLINE
96:9523 Document No.: AIDS-96701605. **Ritonavir/ saquinavir** trial announced. Anonymous. J Int Assoc Physicians AIDS Care (1996). Vol. 2, No. 4, pp. 59. ISSN: 1081-454X. Pub. country: United States. Language: English.
AB Interest in using **ritonavir** and **saquinavir** for combination therapy is high, but the safety of this combination has not been established. Abbott Laboratories released details of a combination therapy trial anticipated to begin in mid-April 1996. One hundred twenty HIV-infected patients will be sequentially tested using four dose combinations. There are concerns that incorrect dose combinations will create dangerous drug levels previously untested in man or will result in suboptimal antiviral efficacy and decreased future response to protease inhibitor therapy.

L84 ANSWER 59 OF 69 AIDSLINE
96:9518 Document No.: AIDS-96701600. **Ritonavir**: first to prolong survival. MacDougall D S. J Int Assoc Physicians AIDS Care (1996). Vol. 2, No. 4, pp. 38-44. ISSN: 1081-454X. Pub. country: United States. Language: English.
AB **Ritonavir** is the first protease inhibitor to demonstrate prolonged survival in advanced HIV disease. The Food and Drug Administration (FDA) approved **ritonavir** in 72 days. **Ritonavir**'s development and clinical testing results are described. Clinical data include **ritonavir**'s use in triple combination therapy with ddC and ZDV, as well as a comparison of its use in monotherapy against ZDV monotherapy and in combination with ZDV. Evidence shows that the use of **ritonavir** increases the duration of patient survival. The potential for cross-resistance to **ritonavir** and a synergistic interaction with **saquinavir** are highlighted.

L84 ANSWER 60 OF 69 AIDSLINE
96:9484 Document No.: AIDS-96701556. **Saquinavir**: combination shows survival benefit; new formulation trial recruiting. Anonymous. AIDS Treat News (1996). no 246, pp. 1-2. ISSN: 1052-4207. Pub. country: United States. Language: English.
AB On May 7, 1996, Hoffmann-La Roche released survival analysis of a major clinical trial comparing its protease inhibitor **saquinavir** (Invirase) plus ddC (Hivid) vs. **saquinavir** alone vs. ddC alone. The combination showed substantial survival benefit. An analysis of disease progression showed a risk reduction of slightly more than one half with the combination. Trial volunteers had baseline CD4 counts between 50 and 300 and had at least 16 weeks of prior treatment with AZT. Only one of the three protease inhibitors, Abbott's **ritonavir** (**Norvir**), previously demonstrated that it reduces disease progression and increases survival. Although the analysis indicates that **saquinavir** did not work well alone, the results may prove different with a higher dose. A trial is enrolling 400 volunteers in 40 sites across the United States. Volunteers must be at least 13 years old, and at least three quarters of those enrolled must not have used any protease inhibitor before. All volunteers will receive the same dose of the new formulation of **saquinavir** for at least 1 year. For more information, individuals may contact the AIDS Clinical Trials Information

Service.

L84 ANSWER 61 OF 69 AIDSLINE
96:8132 Document No.: AIDS-96701523. Protease uninhibited. Anonymous. Notes Undergr (1996). no 32, Suppl., pp. 1-2. Pub. country: United States. Language: English.
AB Three protease inhibitors, indinavir, **ritonavir**, and **saquinavir**, will be available commercially in April 1996. HIV-positive patients should be aware of a number of issues related to their use. All three are effective individually, but they work best in combination with other drugs because the effects are longer-lasting. Resistance to one or all of the protease inhibitors is a risk, and it is essential to continue protease inhibitor therapy once it is started.

L84 ANSWER 62 OF 69 AIDSLINE
96:7215 Document No.: AIDS-96701392. Protease inhibitors: implications for HIV research and treatment. Churchill S A. J Int Assoc Physicians AIDS Care (1996). Vol. 2, No. 1, pp. 13-8. ISSN: 1081-454X. Pub. country: United States. Language: English.
AB Much of the information presented at the Fifth European Conference on Clinical Aspects and Treatment of HIV Infection dealt with HIV protease inhibitors. Pharmacologic, pharmacokinetic, and therapeutic aspects of **ritonavir**, **saquinavir**, and indinavir, given individually, were assessed by both viral load testing and CD4 counts. **Ritonavir**, used in combination with ddC and AZT, reduced HIV RNA and increased CD4 count, with minimal adverse effects. The development of HIV resistance and cross resistance to these protease inhibitors was discussed, with an examination of the number of mutations needed to render the HIV virus resistant. When to begin treatment with these drugs was also a topic of discussion.

L84 ANSWER 63 OF 69 AIDSLINE
96:7133 Document No.: AIDS-96701147. Protease inhibitor update: treatment combination strategies. Mascolini M. AIDS Treat News (1996). no 239, pp. 3. ISSN: 1052-4207. Pub. country: United States. Language: English.
AB Major pharmaceutical manufacturers have agreed that even the most potent protease inhibitors will work more effectively in combination with nucleoside analogs. Protease inhibitors also may be more effective when combined together. A Merck trial indicated that half of the participants taking both AZT and indinavir had viral load reductions below the limit of detection, compared to only thirty percent who used either of the drugs alone. Abbott reported similar findings with **ritonavir**, AZT, and ddC. Glaxo's protease inhibitor, VX-478, has not yet been tested in combination with other drugs. To date, **saquinavir** is the only protease inhibitor to be approved by the Food and Drug Administration (FDA).

L84 ANSWER 64 OF 69 AIDSLINE
96:6809 Document No.: AIDS-96700932. Protease inhibitors and prevention of cross resistance. Levin J. AIDS Treat News (1995). no 232, pp. 1-3. ISSN: 1052-4207. Pub. country: United States. Language: English.
AB A controversy has developed, initiated by a paper in the April 1995 issue of Nature, over the use of protease inhibitors among AIDS patients. The article, written by Jon Condra and Emilio Emini, reported that HIV developed resistance to indinavir (Merck & Co.'s protease inhibitor), and all other protease inhibitors as well. In

response to the study on Merck's product, Roche released information suggesting that their protease inhibitor, **saquinavir**, does not cause resistance nearly as quickly or as much. Merck is currently studying the combination of indinavir and AZT, and Abbott Laboratories is examining the effects of AZT, ddC, and **ritonavir**. These studies imply that optimal multi-drug combination therapy should delay drug resistance as well as cross-resistance. The implications are promising for patients with HIV and AIDS. Pharmaceutical companies are conducting additional studies to develop new reverse transcriptase inhibitors and to determine the effectiveness of the combination of two or more protease inhibitors. Each drug trial demonstrates the relationship between dosing and resistance; patients are advised to adhere completely to dosing instructions.

L84 ANSWER 65 OF 69 AIDSLINE

96:6775 Document No.: AIDS-96700889. Update on HIV protease inhibitors. Vella S. AIDS Clin Care (1995). Vol. 7, No. 10, pp. 79-82, 88. ISSN: 1043-1543. Pub. country: United States. Language: English.

AB When HIV replicates, it forms large precursor proteins that are cleaved and processed by HIV protease to generate smaller viral proteins. HIV protease inhibitors interfere with this process, causing viral particles that are formed to be structurally disorganized, nonfunctional, and non-infectious. All of the HIV protease inhibitors in clinical trials, or nearing clinical development, are active against HIV-1 and HIV-2 at nanomolar concentrations, require no intracellular processing for activation, and are effective both in acutely and chronically infected cells. However, two pharmacokinetic problems have been identified: suboptimal oral bioavailability of peptidic inhibitors; and reduced cellular uptake of inhibitor that has become bound to alpha-acid glycoprotein. Three of the ten aforementioned protease inhibitors are in advanced development: **saquinavir** (**Ro-31 8959**), indinavir (MK-639), and **ritonavir** (ABT-538). **Saquinavir** has been extensively tested. It increases CD4 cell counts, reduces viral load, and its effects are magnified when administered in combination with AZT and ddC. **Saquinavir** recently entered accelerated approval procedures in the United States. Indinavir, an orally bioavailable protease inhibitor, engenders viral resistance after 12-24 weeks when administered at low doses, but higher doses may produce sustained effects lasting 52 weeks. **Ritonavir**, like indinavir, is an orally bioavailable protease inhibitor that is effective for a short time before viral mutants emerge. The emergence of resistance is the greatest problem with protease inhibitors.

L84 ANSWER 66 OF 69 AIDSLINE

96:6387 Document No.: AIDS-96701043. Protease inhibitors. Schouten J T. STEP Perspect (1995). Vol. 7, No. 3, pp. 12-3. Pub. country: United States. Language: English.

AB Protease inhibitors (PRIs) are a diverse group of drugs which block an HIV-1 enzyme needed for the production of new viruses. PRIs stop the production of HIV in newly- or chronically-infected cells. There are currently six PRIs in clinical phase I or II trials: **ritonavir**, indinavir, Invirase, AG1343, U-103017, and VX 478; and there are four newly-identified PRIs soon to begin clinical trials: CGP 53 437, CGP 57 817, **KNI-272**, and A-80978. Eleven monotherapy studies of PRIs presented at the 35th

Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) are described.

L84 ANSWER 67 OF 69 AIDSLINE
96:5270 Document No.: AIDS-96700951. New protease drug shows early promise. Levin J. National AIDS Treatment Advocacy Project, San Francisco, CA. BETA (1995). pp. 27, 33. ISSN: 1058-708X. Pub. country: United States. Language: English.
AB Glaxo Wellcome presented results from evaluation studies on their new protease drug, VX-478, at the Consensus Symposium on Combined Antiviral Therapy in 1995. Results show that VX-478 appears to be synergistic with Roche's Invirase (**saquinavir**), and additive with Merck's Crixivan (indinavir sulfate), and Abbott's **ritonavir**. VX-478 has been shown to be a potent inhibitor of both AZT-sensitive and AZT-resistant viruses. Studies with Merck's Crixivan, another protease inhibitor, indicate problems with cross-resistance; and data on Hoffman-LaRoche's Invirase suggest no cross-resistance problems. It is believed that combination therapy strategies with various protease inhibitors may keep HIV replication in check for a prolonged period, and delay emergence of resistant strains of the virus.

L84 ANSWER 68 OF 69 AIDSLINE
96:5259 Document No.: AIDS-96700940. Abbott agrees to expanded access for **ritonavir**. Baker R. BETA (1995). pp. 4. ISSN: 1058-708X. Pub. country: United States. Language: English.
AB At a meeting with community treatment advocates in Chicago, Abbott Laboratories agreed to expand its access program for **ritonavir** (ABT-538). A complete patient eligibility profile for enrollment in the open label protocol for the drug has not yet been formulated. It appears that in vitro, **ritonavir** increases the concentration of **saquinavir** by 100-fold. Earlier reports of elevated liver enzymes from **ritonavir** are unfounded. Discussions between Roche and Abbott are underway for a clinical study of the double combination of **ritonavir** and **saquinavir**. Roche and Merck are also planning a double combination clinical study of Invirase plus Crixivan.

L84 ANSWER 69 OF 69 AIDSLINE
96:5154 Document No.: AIDS-96700721. Protease inhibitor trials moving to next phase. Anonymous. AIDS Alert (1995). Vol. 10, No. 8, pp. 100-1. ISSN: 0887-0292. Pub. country: United States. Language: English.
AB Hoffmann-La Roche and Agouron Pharmaceuticals are establishing large clinical studies in the United States of their protease inhibitors. La Roche is set to begin its Phase III trial of Invirase (**saquinavir**), which will study the drug alone and in combination with other antiretrovirals. The trial, NV14256, includes 1,000 patients with advanced HIV disease who are no longer tolerant to zidovudine (AZT, Retrovir) and who have a CD4 count between 50 and 300. A concurrent international Phase III trial of **saquinavir** will involve 3,300 patients who have had little or no AZT treatment. Roche will also begin a compassionate-treatment program that will supply **saquinavir** to patients unable to meet the stringent requirements of the clinical trials. Agouron is expected to enter Phase III trials for its protease inhibitor, AG1343. A monotherapy trial will look at optimal dosing, durability, and resistance patterns of the drug. A second trial will combine AG1343 with the antiretroviral, stavudine (D4T). A third trial will

look at the stavudine-AG1343 combination in late-stage patients, and will compare standard-of-care treatment with AG1343 to standard-of-care treatment and placebo. In Agouron's Phase I/II trials for AG1343, results showed up to a 95 percent reduction in viral load throughout the first 4 weeks of treatment for patients. CD4 counts rose as much as 120 in some patients in the first 9 days. Although there is excitement about the four protease inhibitors currently being tested, questions about resistance continue.